Incidence and Duration of Side Effects and Those Rated as Bothersome With Selective Serotonin Reuptake Inhibitor Treatment for Depression: Patient Report Versus Physician Estimate

X. Henry Hu, M.D., Ph.D.; Scott A. Bull, Pharm.D.; Enid M. Hunkeler, M.A.; Eileen Ming, Sc.D.; Janelle Y. Lee, Dr.P.H.; Bruce Fireman, M.A.; and Leona E. Markson, Sc.D.

Background: Selective serotonin reuptake inhibitors (SSRIs) are widely used as the first-line treatment for depression. Information regarding their side effects is mostly based on controlled clinical trials.

Method: Patients who received an SSRI for a new or recurrent case of depression (ICD-9 code 296.2 or 311) between December 15, 1999, and May 31, 2000 were interviewed by telephone 75 to 105 days after initiation of SSRI therapy. Using closed-ended questions, investigators asked patients if they experienced any of 17 side effects commonly associated with SSRIs, how bothersome they were, and what their duration was. Prescribing physicians completed a written survey providing their estimates about frequency of side effects associated with SSRIs and how bothersome those side effects are.

Results: Of 401 patients who completed the phone interview, 344 patients (86%) reported at least 1 side effect, and 219 patients (55%) experienced 1 or more bothersome side effect(s). The most common bothersome side effects were sexual dysfunction and drowsiness (17% each). While most side effects first occurred within the first 2 weeks of treatment, the majority of patients were still experiencing the same side effects at the time of interview, most notably blurred vision (85%) and sexual dysfunction (83%). Overall, physicians (N = 137) significantly underestimated the occurrence of the 17 side effects explored, and they tended to underrate how bothersome those side effects were to their patients.

Conclusion: Side effects associated with SSRIs are common and bothersome to patients. Treatment-emergent side effects tend to persist during the first 3 months of treatment.

(J Clin Psychiatry 2004;65:959–965)

Received Sept. 26, 2003; accepted Jan. 5, 2004. *From Outcomes Research & Management, Merck & Co., Inc., West Point, Pa. (Drs. Hu, Ming, and Markson) and the Division of Research, Kaiser Permanente Medical Care Program, Oakland, Calif. (Drs. Bull and Lee, Ms. Hunkeler, and Mr. Fireman).*

Dr. Bull is currently with ALZA Corporation, Mountain View, Calif. This research was completed while Dr. Bull was working at the Kaiser Permanente Division of Research.

This study was financially supported by Merck & Co., Inc., Whitehouse Station, N.J.

Drs. Hu, Ming, and Markson are employees of Merck. Dr. Bull has received grant/research support from Merck. Ms. Hunkeler, Dr. Lee, and Mr. Fireman have received grant/research support from Eli Lilly.

Corresponding author and reprints: X. Henry Hu, M.D., Ph.D., Outcomes Research & Management, Merck & Co., Inc., P.O. Box 4, WP39-130, West Point, PA 19486 (e-mail: Henry_Hu@Merck.com).

Depression is the most commonly occurring mental disorder. It affects over 10% of the population each year.[1] When the selective serotonin reuptake inhibitors (SSRIs) were introduced, they quickly replaced tricyclic antidepressants (TCAs) and other antidepressants as the first line of therapy, mostly because they had a safer margin in overdose and seemed to be better tolerated.[2,3] Although it is believed that SSRIs as a class hold significant advantages over TCAs for managing most depressive patients, many patients receiving SSRIs still experience significant side effects. Results from a recent meta-analysis of clinical trial data comparing adverse effects associated with SSRIs and TCAs indicate that both classes of drugs are associated with significant side effects, although the key effects differ. The authors noted that SSRIs precipitate some adverse effects significantly more often than TCAs do, including nausea, anorexia, diarrhea, insomnia, nervousness, anxiety, and agitation. Other adverse effects that occur significantly less frequently with SSRIs are mainly anticholinergic symptoms such as dry mouth, constipation, dizziness, sweating, and blurred vision.[4]

Successful management of depressive patients on antidepressant treatment requires continuation of drug therapy for 16 to 20 weeks after remission of depressive symptoms to prevent relapse. Maintenance treatment should be considered for patients at high risk for relapse.[5–9]

Both clinical trials and "real world" studies consistently show that poor tolerability is associated with increased discontinuation of drug therapy.[10,11] Therefore, the choice of a specific agent is strongly influenced by its side effects profile and tolerability.[12,13] Furthermore, guidelines by the American Psychiatric Association[5] stress the importance of monitoring side effects over the course of treatment and informing patients of potential side effects including those that require immediate attention. Communication about antidepressant medications has been shown to improve adherence to treatment.[14]

For these reasons, it is important that physicians have a complete understanding of the side effects associated with each class of antidepressant in order to increase the likelihood that their patients are treated with the right medication at the right dose for the appropriate duration. However, physicians' knowledge about the untoward effects of antidepressants may be based primarily on results of clinical trials, and it is well known that adverse events observed in clinical trials may not reflect adverse experiences of patients in real world settings who take the drugs for an extended period of time.[15,16] In addition, underreporting of drug-related side effects to physicians is likely to be more widespread in patients with depression than other disorders because such patients are unlikely to proactively seek help during the course of treatment even if they have experienced drug-related adverse effects. Lastly, because about half of depressed patients receive care only in the primary care setting and 77% of all antidepressant prescriptions are written by primary care providers,[2,17] there may be limited time for patients to discuss side effects during follow-up appointments.

In this article, we describe the incidence, discomfort, and duration of SSRI-related side effects in a sample of Health Maintenance Organization (HMO) patients newly treated with SSRIs over the first 3 months of their treatment for depression. We also contrast patients' actual reporting of side effects with physicians' perceptions of the frequency of and discomfort caused by these side effects. For the reasons described above, we were interested in determining whether physicians would underestimate the incidence of commonly reported SSRI side effects and how bothersome they are to patients.

METHOD

The study was conducted at the Northern California Kaiser Permanente Medical Care Program, Oakland, which serves over 3 million members at 16 medical centers and 27 outpatient facilities. Health plan databases were used to identify potential study participants who received an SSRI for a new or recurrent case of depression between December 15, 1999, and May 31, 2000. Patients were eligible if they had recently begun a treatment regimen of SSRI antidepressant (at least a 6-month interval since any previous antidepressant treatment); received a diagnosis of major depressive affective disorder or depressive disorder, not elsewhere classified (ICD-9 code 296.2 or 311, respectively) within 30 days of the date medication was dispensed; were 18 to 75 years of age; had no concurrent comorbidity of bipolar disorder, bulimia, eating disorder, dementia, chemical dependency, or psychotic disorders; and did not have the diagnosis of cancer, acute myocardial infarction, or stroke recorded in the health plan's databases.

Patient Interview

Telephone interviews were conducted within 75 to 105 days of starting antidepressant therapy, after treating physicians gave permission for patients to be contacted about the study. After confirming that the patient had begun taking the antidepressant as recorded in the administrative database, interviewers read a list of 17 side effects commonly associated with SSRIs and asked the patients (yes/no) whether they had experienced any of them while they were treated with the first antidepressant prescribed. For each side effect reported by a patient, additional questions were asked to determine when they first experienced it (during the first 1–2 weeks, during weeks 3–4, after 4 weeks of treatment) and whether they were still experiencing it at the time of the survey (yes/no). Patients were also asked if they thought the side effect was related to the SSRI and to characterize how bothersome the side effect had been to them using a 4-point scale (1 = not bothersome at all; 2 = somewhat bothersome; 3 = a lot bothersome; 4 = extremely bothersome). Lastly, patients who had experienced more than 1 side effect were asked to rank which side effect was most bothersome to them. All patients were also asked if they had discussed side effects with their physician since starting the antidepressant. The questionnaire was pilot-tested with 22 eligible patients, and the Kaiser Foundation Research Institute Institutional Review Board approved the study.

Physician Survey

The physicians who had prescribed an SSRI for study participants were asked to complete a written questionnaire in which they were asked questions about side effects that were analogous to those asked of patients. Instead of asking whether study participants had experienced side effects, physicians were asked to estimate the percentage of their patients who experienced each of the 17 side effects when starting therapy with an SSRI using a visual analog scale from 0% to 100% with dispersed anchor points of 10%. Similarly, they were asked to estimate how bothersome each of the 17 side effects was believed to be to their patients using the same 4-point scale provided for patients. Physicians were also asked whether they routinely discussed potential side effects with their patients during follow-up visits. The physician survey

was pilot-tested with 6 psychiatrists and 6 primary care physicians.

Statistical Analysis

Due to the clustered nature of the data at the physician level, arising from multiple patients being treated by the same physician, we evaluated the extent of the cluster effect on the response variable (frequency of reported side effects). We computed the intraclass correlation that compares within-physician variation with across-physician variation and concluded that clustering effect was not a significant issue and treated observations within a physician as independent from each other. Furthermore, because physicians were not asked about a specific patient's experience, but rather about SSRI-related side effects in general, we treated the 2 populations as independent and used a binomial test for each side effect. We tested whether the average observed frequency of a particular side effect reported by patients was greater than what physicians estimated and adjusted the p values for multiplicity using the Bonferroni method. Additionally, in order to make an overall statement about the discrepancy between patients' experiences and physicians' perceptions of the frequency of side effects, we employed the Fisher method[18] to combine p values into 1 overall p value. The overall p value pertains to test of differences in the frequency of side effects in general as opposed to particular side effects.

Because only bothersome side effects were associated with premature discontinuation of antidepressant therapy,[14] we present the percentage of each side effect reported by patients as bothersome (defined as "a lot bothersome" or "extremely bothersome") and estimated by their physicians, respectively.

When a patient reported an adverse event but was unsure if it was caused by the index medication, we did not count it as a side effect in the tabulation and data analysis.

RESULTS

During the study period, a total of 765 patients were contacted. We excluded 260 patients as follows: 40 (15%) never started taking the medication, 36 (14%) had taken an antidepressant within 6 months before the index date, 17 (7%) did not speak English, 97 (37%) could not be reached by telephone within 4 months of starting treatment (with at least 3 attempts), and 31 (12%) were unable to respond to the survey for reasons such as inability to concentrate. Eligibility could not be determined for 39 (15%) of the patients contacted. Of the remaining 505 eligible patients, 401 (79%) completed the telephone survey. Among them, 79 (20%) had discontinued antidepressant therapy and 54 (13%) switched to another antidepressant. The physician survey questionnaire was completed by 137 (82%) of the 167 physicians who treated 1 or more of the study participants. Two thirds of physicians were family physicians or internists and the remaining one third were psychiatrists. Most physicians (77%) had been in practice more than 5 years since their residency training.

Table 1. Characteristics of Study Patients (N = 401) Taking SSRIs for Depression

Characteristic	Mean	SD
Age, y	45.8	15.5
	N	%
Female gender	284	70.8
SSRI prescribed[a]		
Paroxetine	200	50.0
Fluoxetine	172	43.0
Sertraline	15	3.8
Citalopram	13	3.2
Prior antidepressant use		
Yes	156	38.9
No	241	60.1
Don't know	4	1.0
Race		
White	267	66.5
Black	36	9.0
Latino or Hispanic	42	10.5
Other	56	14.0
Marital status		
Married	215	53.6
Single	64	16.0
Separated, divorced, or widowed	119	29.7
Don't know or refused	3	0.7
Education		
≤ High school	116	28.9
Some college	154	38.4
College or graduate	130	32.4
Don't know or refused	1	0.3
Employment status		
Employed	249	62.1
Unemployed/homemaker/student/retired	141	35.2
Don't know or refused	11	2.7

[a]One patient missing information.
Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

Table 1 presents the demographic characteristics of the study population. Thirty-nine percent of patients reported that they had previously taken antidepressant drugs but not within the 6 months prior to entering the study, and 93% were prescribed either paroxetine or fluoxetine. Mean age of study participants was 46 years, and women accounted for 71% of the study population. About two thirds of participants classified themselves as white, and slightly over half were married at the time of interview. About one third had at least a college degree, and 62% were currently employed.

Not counting treatment-emergent side effects that patients were not sure were drug-related, 344 patients (86%) reported at least 1 side effect, and 208 (52%) reported 3 or more side effects. When only bothersome side effects were considered, 219 patients (55%) experienced 1 or more bothersome side effects, and 69 patients (17%) experienced 3 or more bothersome side effects.

Table 2 shows the incidence of the 17 side effects commonly associated with SSRI treatment over the 3-month observation period. The most common side effect reported by patients was drowsiness (38.4%), followed by

Table 2. Incidence of All Side Effects and Bothersome Side Effects During the First 3 Months of SSRI Treatment for Depression (N = 401)[a]

	Frequency of Side Effects		Frequency of Bothersome Side Effects[b]	
Side Effect	N	%	N	%
Drowsiness	154	38.4	66	16.5
Sexual dysfunction	136	33.9	67	16.7
Dry mouth	136	33.9	26	6.5
Headache	94	23.4	40	10.0
Dizziness	92	22.9	43	10.7
Insomnia	90	22.4	45	11.2
Anxiety	77	19.2	44	11.0
Nausea	70	17.5	23	5.7
Weight gain	69	17.2	46	11.5
Tremors	62	15.5	19	4.7
Diarrhea	60	15.0	10	2.5
Constipation	50	12.5	19	4.7
Rash or itching	46	11.5	24	6.0
Weight loss	45	11.2	5	1.2
Stomach upset	44	11.0	13	3.2
Blurred vision	44	11.0	22	5.5
Swelling	22	5.5	6	1.5

[a]Only those side effects that patients attributed to the antidepressant initially prescribed are included.
[b]Defined as "a lot bothersome" or "extremely bothersome."
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 3. Onset and Duration of Side Effects Associated With SSRIs During the First 3 Months of Treatment for Depression (N = 401)

Side Effect	N	Occurred During the First 2 Weeks, %	Continued to Experience at 3-Month Interview, %[a]
Drowsiness	154	69.9	62.9
Sexual dysfunction	136	69.9	83.3
Dry mouth	136	84.6	68.3
Headache	94	66.0	64.5
Dizziness	92	71.7	53.3
Insomnia	90	64.4	56.4
Anxiety	77	71.4	48.7
Nausea	70	82.9	32.5
Weight gain	69	29.0	59.6
Tremors	62	59.7	71.1
Diarrhea	60	78.3	45.0
Constipation	50	64.0	77.4
Rash or itching	46	32.6	75.8
Weight loss	45	44.4	40.6
Stomach upset	44	65.9	28.0
Blurred vision	44	59.1	84.6
Swelling	22	31.8	88.2

[a]Patients who had discontinued index medication (N = 133) were not included.
Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

dry mouth and sexual dysfunction (34.0% each). When only bothersome side effects were considered, sexual dysfunction (16.7%) was the most commonly reported, followed by drowsiness (16.5%) and weight gain (11.5%).

To assess how bothersome these side effects were in relation to each other, we asked patients who experienced more than 1 side effect to rank which side effect was the most bothersome to them. For the 266 patients who reported more than 1 side effect, sexual dysfunction was rated the most bothersome side effect by 16.9% of patients, and drowsiness was the second most bothersome at 12.4%.

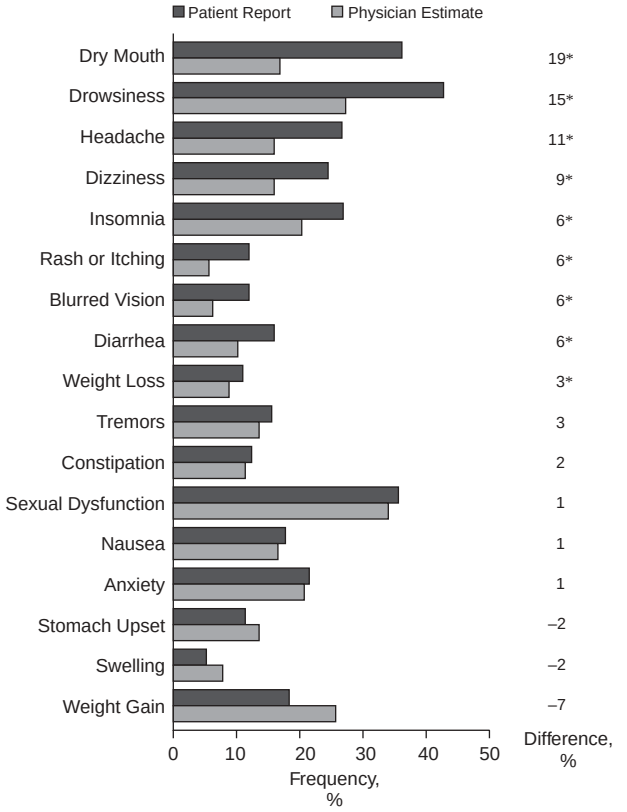
Table 3 presents the time that patients first started to experience a specific side effect after initiation of drug therapy and whether they were still experiencing the same side effect at the time of the interview. Most side effects emerged within the first 2 weeks of treatment with exception of rash/itching, swelling, and weight gain/loss, which frequently occurred later. Most patients who reported side effects were still experiencing the same ones at the time of the telephone interview (excluding those patients who had discontinued index medication), most notably swelling (88%), blurred vision (85%), and sexual dysfunction (83%).

About 54% of physicians reported that they routinely discussed SSRI-related side effects with all of their patients during follow-up visits. When patients were asked a similar question, 48% recalled having such a discussion over the course of treatment. Figure 1 displays the incidence of each of the 17 side effects that were estimated by physicians in comparison with those reported by patients. Physicians significantly underestimated the frequency of occurrence for 9 of the side effects (dry mouth, drowsiness, headache, dizziness, insomnia, rash or itching, blurred vision, diarrhea, and weight loss). Pooling individual p values together to test the overall differences in the frequency of side effects reported by patients compared with that estimated by physicians was also statistically significant ($p < .001$), indicating that physicians overall tended to significantly underestimate the occurrence of SSRI-related side effects. Figure 2 illustrates the percentage of each side effect reported as bothersome by patients and estimated as such by their physicians. With the exception of sexual dysfunction and drowsiness, physicians underrated the level of discomfort of the remaining 15 side effects. The discomfort caused by blurred vision and constipation were the most underestimated by physicians: 50% of patients reported blurred vision as bothersome vs. the physicians' estimate of 23%; 38% of patients reported constipation as bothersome vs. the physicians' estimate of 9%.

DISCUSSION

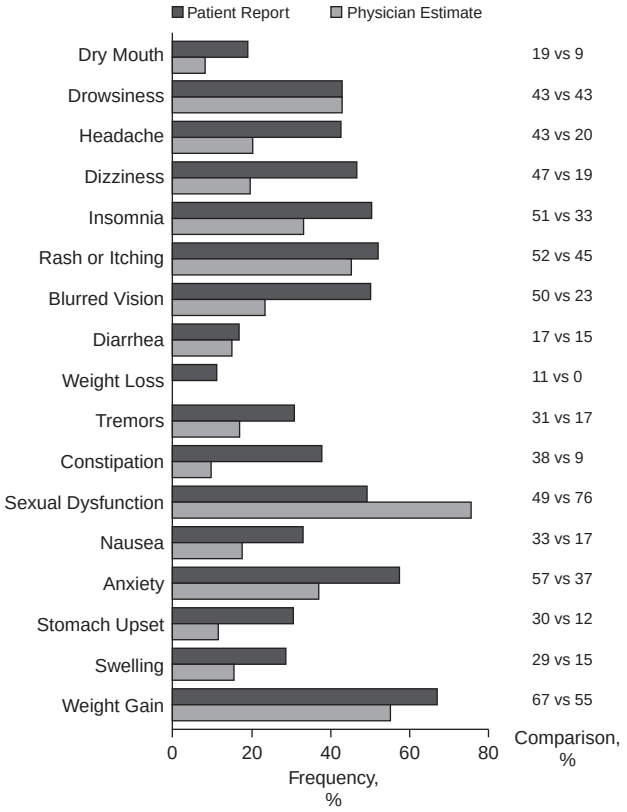
In this HMO-based survey of depressed patients newly treated with an SSRI, we observed that 4 of 5 patients experienced 1 or more side effects, and over half experienced at least 1 side effect that was considered to be quite bothersome. Patients in this real-world-setting study reported a higher incidence of drug-related side effects than those patients who participated in clinical trials,[19] most notably drowsiness, sexual dysfunction, dry mouth, and upper gastrointestinal disturbances. Although it is ex-

Figure 1. Difference in Frequency of Side Effects Associated With SSRI Treatment: Patient Report Versus Physician Estimate



*Significantly underestimated by physicians ($p < .05$).
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 2. Percentage of SSRI-Related Side Effects Rated as Bothersome ("a lot" or "extremely") by Patients and Their Physicians



Abbreviation: SSRI = selective serotonin reuptake inhibitor.

pected that most side effects appear within the first 2 weeks of treatment, we were surprised to find that most patients were still experiencing many of the same side effects 3 months after the initiation of therapy.

Among the side effects studied, drowsiness and sexual dysfunction appeared to be the most problematic for patients. These side effects were experienced by over one third of the patients, and nearly half of them felt that these side effects were "a lot" or "extremely" bothersome. In addition, sexual dysfunction followed by drowsiness were ranked as the most bothersome side effects by patients who reported experiencing 2 or more side effects. In contrast, about the same number of patients experienced dry mouth, but only 19% felt that it was "a lot" or "extremely" bothersome. Distinguishing bothersome side effects from less troublesome ones is important because bothersome or severe side effects are significantly associated with treatment discontinuance.[14–17,19,20]

It is worth mentioning that data from product inserts approved by the U.S. Food and Drug Administration for SSRIs point to a much lower frequency of sexual dysfunction than we observed.[21] Using a validated sexual dysfunction questionnaire, Montejo et al.[22] estimated that sexual dysfunction occurs in 58% to 73% of patients taking SSRIs. Although we did not use a sexual dysfunction questionnaire in our study, we asked patients directly if they had sexual dysfunction without providing a specific definition or clarification of what that means. Nevertheless, our incidence rate of sexual dysfunction appeared to be very close to rates published in the literature, which most authors have found to be 20% to 45%.[21,23–27]

Previous research on fluoxetine has shown that the first appearance of side effects generally occurs during the first week of treatment. For activating types of events such as agitation, anxiety, nervousness, and insomnia, persistent occurrences tended to decline at 5 to 6 weeks.[28] In our study, we observed that most patients started to experience side effects during the first 2 weeks of treatment. But we did not expect so many patients to continue to be bothered by the same side effects 3 months after the initiation of the therapy, as many of these side effects were previously believed to be transient. This observation also has important implications for depression care since many patients may no longer suffer from depressive symptoms

after 3 months of pharmacotherapy. One of the important roles of the physician is to encourage patients to stay on drug therapy to prevent relapse or recurrence. Patients continuously experiencing side effects may be particularly reluctant to undergo treatment during an asymptomatic period, and their attitudes may influence physicians' decisions to pursue therapy aggressively.[29]

Comparison of frequency of common side effects and how bothersome they are to patients as perceived by physicians and as reported by patients showed mixed results. On the one hand, physicians were conversant with common types of SSRI-related side effects, as their estimates for the relative frequency of each symptom mirrored what was reported by patients, including sexual dysfunction. On the other hand, they tended to underestimate how bothered patients were by these side effects. This may be the result of poor communication between patients and physicians after the initiation of therapy. Among this cohort of study patients, only half reported having discussions with their physicians about side effects within the first 3 months of treatment. It is unknown if patients failed to volunteer information about the side effects they were experiencing or if physicians failed to ask patients to report information about their side effects. Either situation would contribute to physicians' lack of understanding of the true incidence of side effects experienced by their patients and how bothersome those side effects are.

Two factors may have contributed to the higher incidence of side effects in our study. We asked patients directly about the occurrence of specific side effects they may have experienced using close-ended questions. This may facilitate patient recall of past experiences. Patients may also have been more open to reporting their experiences when the questions were asked by someone unknown to them. Because patients may find it difficult to distinguish between the effects of the disease versus the effects of drugs, we purposely asked them if they believed the side effects were caused by the index medication and excluded all side effects patients did not attribute to the SSRIs. This is in contrast to adverse events reported in clinical trials, which usually include all treatment-emergent events regardless of causality. In our study, about a quarter to nearly half of treatment-emergent–specific adverse events were not counted because patients were not sure whether or not they were drug-related.

There are some limitations to our study. The findings were based entirely on the ability of patients to recall events or conversations over a 3-month period. By the nature of voluntary participation, patients experiencing the untoward effects of the medication may have been more interested in participating in the study and more motivated to report side effects. We also only recruited patients whose physicians granted us permission to contact their patients. Although this permission was obtained for 73% of potentially eligible study participants, we do not have information as to why some patients were precluded from participation.

In conclusion, among patients newly treated with SSRIs, over half experienced at least 1 bothersome side effect, and, in most cases, patients continued to experience the same side effects 3 months after start of drug therapy. Both sexual dysfunction and drowsiness were frequently reported as bothersome side effects. Overall, physicians were knowledgeable about SSRI-related side effects, although they tended to underestimate their frequency and how bothersome they were to patients. Physicians should more proactively manage the drug-related side effects through determination of their presence, evaluation of their causes, and implementation of appropriate interventions without compromising the treatment of depression.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft).

REFERENCES

1. Kessler RC, Zhao S, Katz SJ, et al. Past year use of outpatient services for psychiatric problems in the National Comorbidity Survey. Am J Psychiatry 1999;156:115–123
2. Way K, Young CH, Opland E, et al. Antidepressant utilization patterns in a national managed care organization. Drug Benefit Trends 1999;1: 6BH–11BH
3. Henry JA. Toxicity of antidepressants. Int Clin Psychopharmacol 1992;6(suppl 4):43–51
4. Trindade E, Menon D, Topfer LA, et al. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. CMAJ 1998:159:1245–1252
5. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. Am J Psychiatry 2000;157(suppl 4):1–45
6. Reimherr FW, Amsterdam JD, Quitkin FM, et al. Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. Am J Psychiatry 1998;155:1247–1253
7. Melfi CA, Chawla AJ, Croghan TW, et al. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. Arch Gen Psychiatry 1998;55:1128–1132
8. Reynolds CF III, Frank E, Perel JM, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA 1999;281:39–45
9. Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. JAMA 1998;280:1665–1672
10. Hotopf M, Hardy R, Lewis G. Discontinuation rates of SSRIs and tricyclic antidepressants: a meta-analysis and investigation of heterogeneity. Br J Psychiatry 1997;170:120–127
11. Linden M, Gothe H, Dittmann RW, et al. Early termination of antidepressant drug treatment. J Clin Psychopharmacol 2000;20:523–529
12. Clinical Practice Guideline Number 5: Depression in Primary Care, vol. 2. Treatment of Major Depression. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; 1993. AHCPR publication 93-0551
13. American Psychiatric Association. Practice Guideline for Major Depressive Disorder in Adults. Am J Psychiatry 1993;150(suppl 4):1–26
14. Bull SA, Hu X, Hunkeler EM, et al. Antidepressant discontinuation and switching: influence of patient-provider communication. JAMA 2002;288:1403–1409
15. Schafer H. Post-approval drug research: objectives and methods. Pharmacopsychiatry 1997;30(suppl 1):4–8
16. Rogers AS. Adverse drug events: identification and attribution. Drug Intell Clin Pharm 1987;21:915–920

17. Katon W, Robinson P, Von Korff M, et al. A multifaceted intervention to improve treatment of depression in primary care. Arch Gen Psychiatry 1996;23:924–932
18. Fisher RA. Statistical Methods for Research Workers. 14th ed. New York, NY: Hafner Press; 1970
19. Nelson JC. Safety and tolerability of the new antidepressants. J Clin Psychiatry 1997;58(suppl 6):26–31
20. Bull SA, Hunkeler EM, Lee JY, et al. Discontinuing or switching selective serotonin-reuptake inhibitors. Ann Pharmacother 2002;36:578–584
21. Dewan MJ, Anand VS. Evaluating the tolerability of the newer antidepressants. J Nerv Ment Dis 1999;187:96–101
22. Montejo AL, Llorca G, Izquierdo JA, et al, for the Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. J Clin Psychiatry 2001;62(suppl 3):10–21
23. Balon R, Yeragani VK, Pohl R, et al. Sexual dysfunction during antidepressant treatment. J Clin Psychiatry 1993;54:209–212
24. Jacobsen FM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. J Clin Psychiatry 1992;53:119–122
25. Modell JG, Katholi CR, Modell JD, et al. Comparative sexual side effects of bupropion, fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997;61:476–487
26. Benazzi F, Mazzoli M. Fluoxetine-induced sexual dysfunction: a dose-dependent effect? Pharmacopsychiatry 1994;27:246
27. Richelson E. Pharmacology of antidepressants: characteristics of the ideal drug. Mayo Clin Proc 1994;69:1069–1081
28. Beasley CM, Sayler ME, Weiss AM, et al. Fluoxetine: activating and sedating effects at multiple fixed doses. J Clin Psychopharmacol 1992; 12:328–333
29. Phillips LS, Branch WT Jr, Cook CB, et al. Clinical inertia. Ann Intern Med 2001;135:825–834