Evaluation of Resources Used To Treat Adverse Events of Selective Serotonin Reuptake Inhibitor Use

by Karen Rascati, Paul Godley, and Hoa Pham

OBJECTIVE: To assess the frequency and the costs of adverse events associated with selective serotonin reuptake inhibitor (SSRI) treatment.

DESIGN: Electronic medical records and medication profiles were retrospectively reviewed.

PATIENTS: Patients over 18 years old with a new prescription for an SSRI who were continuously enrolled for at least one year and who had a diagnosis of depression.

MAIN OUTCOME MEASURES: The perspective was that of the managed care organization (MCO); therefore, only direct medical costs were measured.

RESULTS: Of the 337 patients who met the inclusion criteria, about 40% (137 patients) had at least one side effect associated with an SSRI noted in their medical record. The most common adverse events reported were sleep problems, gastrointestinal (GI) upset/nausea/diarrhea, and fatigue/low mental alertness. A total of 96 patients (28%) had 101 medication changes made after initial therapy,

including 33 additions of medication, 31 switches to another antidepressant, 28 discontinuations of therapy due to adverse events, and 9 dose changes. Costs to treat adverse events included medication changes (n=101), physician visits (n=32), lab tests for dosage adjustments (n=6), and emergency room visits (n=3). Sensitivity analyses indicated that the direct medical costs associated with the treatment of adverse events ranged from approximately \$11–\$17 per patient. There were no statistical differences in utilization patterns, overall frequency of adverse events, or costs of adverse events between the SSRIs compared in this study.

CONCLUSIONS: Although 40% of patients noted at least one side effect of the treatment, the direct medical costs associated with the adverse events were relatively small. Future studies might investigate the indirect and intangible costs of these adverse events.

KEYWORDS: SSRI, adverse events, antidepressants, costs

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Depressive disorders are among the most common illnesses seen in the general medical setting. More than 10% of the population suffers from depression at any given time.¹ An article published in 1993 estimated the cost of depression at \$44 billion annually. Of this amount, \$12 billion is attributable to direct medical costs (hospitalizations, medications, physician visits) while the remaining \$32 billion is attributable to indirect costs (absenteeism, decreased productivity, deaths from suicide).² Research on compliance reported that patients take approximately 65% of the recommended amount of antidepressant medication, with a range of 40%–90%.³ Some adverse events from the selective serotonin reuptake inhibitor (SSRI) class of antidepressants include increased anxiety (5%–8%), asthenia/fatigue (9%–15%), diarrhea (12%–24%), dry mouth (10%–18%), insomnia (13%–28%), nausea (21%–30%), somnolence (13%–23%), and sexual dysfunction (13%–17%).^{4,5} Because of the adverse events associated with SSRI use, additional therapies (medications and/or medical visits) are used to counteract some of these adverse events, which, in turn, contribute to an increase in direct medical costs.

The goals of this research were to use prescription claims data combined with electronic medical record (EMRx) chart review to measure the number and type of adverse events seen with each SSRI in the management of depression, and to estimate the costs associated with treating these adverse events.

This study was done from the perspective of the Scott and White Health Plan (SWHP). Therefore, only direct medical costs to SWHP will be measured.

Methods

SWHP is an integrated health care network located in Temple, Texas. It serves many cities in central Texas and has more than 170,000 members. More than one million patient visits are recorded each year. SWHP has an electronic medical record (EMRx) system that contains information for each patient visit in a searchable electronic database.

Data from 1998–1999 prescription claims were used for the analyses. Data on each patient in the SWHP database who had received an SSRI of interest (paroxetine, fluoxetine, or sertraline) in the last quarter of 1998 were extracted from the prescription database. The first day that an SSRI prescription was filled was termed the patient's index date. Patient information was included if the following criteria were met:

- Patient was over 18 years old.
- Patient was continuously enrolled for the 12-month time

TABLE 1 Types of Adverse Events

Side Effect Documented	Paroxetine n (% of 17)	Fluoxetine n (% of 83)	Sertraline n (% of 237)	Total N (% of 337)
Sleep disturbances	3 (17.6)	11 (13.2)	26 (11.0)	40 (11.9)
GI disturbances/ nausea/diarrhea	1 (5.9)	4 (4.8)	26 (11.0)	31 (9.2)
Nonspecific (did not feel well, malaise) or not specified	1 (5.9)	3 (3.6)	19 (8.0)	23 (6.8)
Trouble focusing/low mental alertness/fatigue/light-headedness	—	3 (3.6)	13 (5.5)	16 (4.7)
Feeling jittery/anxiety/sweating/ palpitations	—	2 (2.4)	13 (5.5)	15 (4.5)
Appetite/weight change	—	5 (6.0)	10 (4.2)	15 (4.5)
Sexual dysfunction	2 (11.8)	2 (2.4)	8 (3.4)	12 (3.6)
Headache	—	3 (3.6)	8 (3.4)	11 (3.2)
Other adverse events	2 (11.8)	1 (1.2)	15 (6.3)	18 (5.3)
Total	9 (52.9)	34 (40.9)	138 (58.2)	181 (53.7)

TABLE 2 Medication Changes due to Adverse Events

Type of Medication Change	Paroxetine n=17	Fluoxetine n=83	Sertraline n=237	Total N=337
Drug added	4	5	24	33
Switch	3	6	22	31
Drug discontinued	1	7	20	28
Dosage changed	0	3	6	9
Total	8	21	72	101
Patients with <i>at least one</i> medication change	8 (47.1%)	19 ^a (22.9%)	69 ^a (29.1%)	96 ^a (28.5%)

^aThis number is lower than the column total because some patients had more than one change to their drug therapy.
Chi-square=No significant difference between index drugs

frame (six months before the index date and six months after the index date).

- Patient started a new prescription for an SSRI during the period of interest. These patients had no antidepressant medication listed in their prescription records for at least six months before their index date.
- Patient's EMRs included a diagnosis of depression.

Electronic Medical Record Database Extraction

Patient records that matched the criteria listed above were retained in the study. Medical record numbers for these patients were used to access their electronic EMRs. Reviewing EMRs is

similar to conducting chart reviews, except that the information has been dictated into an electronic format, allowing researchers to search for key terms. Records for 10% of the sample were reviewed by two researchers to check for inter-rater reliability.

EMRs were reviewed to determine whether a diagnosis was recorded for the index SSRI prescription. If the recorded diagnosis included the word "depression" (including dual diagnoses such as depression and anxiety), patients were retained in the study. Records of patients who met all four criteria were then reviewed to determine if any adverse events due to an SSRI were reported and recorded in the patient's EMR. The number and types of adverse events were categorized and information on

TABLE 3 Medical Visits Due to Adverse Events

Type of Utilization	Paroxetine n=17	Fluoxetine n=83	Sertraline n=237	Total N=337
Physician office visit	3	7	22	32
Emergency department visit	—	1	2	3
Lab test	1	—	5	6
Total	4	8	29	41
Patients with at least one medical visit	3 ^a (17.6%)	7 ^a (8.4%)	26 ^a (11.0%)	36 ^a (10.7%)

^aThis number is lower than the column total because some patients had more than one medical visit. Chi-square=No significant difference between index drugs.

TABLE 4 Direct Medical Cost Estimates

	Paroxetine n=17	Fluoxetine n=83	Sertraline n=237	Total N=337
Average increase in prescription costs	\$16.95	\$4.90	\$2.32	\$3.69
Average increase in medical costs—low estimate	\$10.29	\$6.62	\$6.85	\$6.97
Average increase in medical costs—high estimate	\$18.24	\$12.35	\$12.87	\$13.01
Average increase in total costs—low estimate	\$27.24	\$11.52	\$9.17	\$10.66 ^a
Average increase in total costs—high estimate	\$35.19	\$17.25	\$15.19	\$16.70 ^a

^aANOVA found no significant difference between index drugs for total increase in costs.

resources used to treat these adverse events was collected. Resources used to treat adverse events included other medications and medical service visits (e.g., physician visits, emergency department [ED] visits, and laboratory services).

Cost Estimates

Because the perspective of this study was that of the health plan, reimbursement amounts for the medications and medical services (i.e., direct medical costs) by this plan were used. Medication costs were obtained directly from each patient's prescription records, and consisted of the amount actually paid to pharmacies by the health plan. Estimated average costs were used to quantify resources used for medical services (physician visits, labs, and ED visits). Because this retrospective study covered data for one year, adjustments and discounting of these costs were not needed. A sensitivity analysis was performed by varying estimated medical service costs within a reasonable range.

Statistical Analysis

Demographic and outcome variables were compared for the three SSRIs studied using a commercial statistical package, SAS 8.0.⁶ Chi-square analyses were used to compare categorical variables,

and analysis of variance (ANOVA) procedures was used for continuous variables. An alpha level of 0.05 was used to test for significance.

Results

An analysis of the SWHP prescription database indicated that a total of 464 patients met the first three criteria (over 18 years old, continuously enrolled, and started a new SSRI in the last quarter of 1998). Medical record numbers for these 464 patients were obtained from SWHP and each patient's electronic medical record was searched in order to determine the reason for the SSRI prescription. Only 73% (N=337) of the medical records for these patients listed a diagnosis of depression; 16% (n=73) had diagnoses other than depression that may have triggered the prescribing of an SSRI (e.g., premenstrual dysphoric disorder or anxiety); 11% (n=54) showed no diagnosis in the record to indicate the reason for prescribing an SSRI. Therefore, 337 patients met all four criteria: 17 (5%) with paroxetine as their index drug, 83 (25%) with fluoxetine as their index drug, and 237 (70%) with sertraline as their index drug. Inter-rater reliability of data collected from the electronic medical records was 100%.

Approximately 70% of the sample was female and the average age was 50 years old (age range was 19–92 years old). There were no significant differences in gender by drug, but patients started on paroxetine were, on average, older than patients on the other two SSRIs (paroxetine=60 years old, fluoxetine=48 years old, sertraline=50 years old; ANOVA, $p=.03$).

Adverse Events

Patients' electronic medical records (EMRs) were searched for six months after their index date to determine whether an adverse event attributed to an SSRI was noted. Of the 337 patients in the sample, 137 (40.7%) had at least one adverse event due to their index SSRI documented in their EMRs. There was no significant difference in the percentage of patients with at least one adverse event by index drug. These 137 patients had 181 adverse events listed in the medical records (some had more than one complaint). The specific types of adverse events are listed in Table 1, page 403.

Treatment of Adverse Events: Medications

A total of 96 patients (28.5%) had 101 changes made to their medication therapy because of adverse events over the six-month follow-up period (see Table 2, page 403). There were no significant differences in the percentage of patients with medication changes by index drug. Thirty-three patients had medications added because of adverse events with the index SSRIs. Added medications included trazodone ($n=9$); anxiolytics, such as alprazolam ($n=8$); tricyclic antidepressants (TCAs), such as amitriptyline ($n=6$); sleep medications, such as temazepam ($n=5$); and gastrointestinal medications, such as Imodium ($n=5$). Thirty-one patients were switched to another antidepressant. Most patients were switched from one index drug to another ($n=12$); seven were switched to bupropion; five were switched to venlafaxine; three were switched to a TCA; two to trazodone; one to citalopram; and one to nefazodone. Twenty-eight patients discontinued their index drug and were not put on another antidepressant. Nine patients had the dose of their index drug decreased because of an adverse event.

Treatment of Adverse Events: Medical Services

Table 3, page 404, lists medical visits associated with SSRI adverse events. Thirty-two patients had an office visit due to an adverse event. At most of the office visits, a medication change was made to the patient's regimen. Three patients visited the ED. One visit occurred after a patient took an overdose (10 times the daily dose) of the index drug; another patient felt too drowsy when taking her medication, so she discontinued it and came to the ED when her depression returned; and another patient presented at the ED with "chills, tremor, and feeling numb all over." Six laboratory tests were ordered due to SSRI treatment. One was a liver-function test and five were TSH (thyroid stimulation hormone) tests.

Costs of Treating Adverse Events

Table 4, page 404, lists the costs of medication and medical visits used to treat adverse events in the six months after the index date. In order to estimate the cost of medication changes, actual reimbursement amounts were taken directly from the prescription records for each patient. Sometimes a change in medication could result in no increase in costs (e.g., switching to a similarly priced medication). Also, if over-the-counter (OTC) medications (e.g., Imodium) were used to treat adverse events, this cost was not included because SWHP was not charged for OTCs. Only 32 patients had direct medical costs associated with a medication change. The lowest cost was \$4.51 for one added alprazolam prescription; the highest cost was \$246.33 for six added prescriptions for bupropion. The total medication cost for the changes for these 32 patients was about \$1,244 (mean for these 32 patients=\$39, median=\$24; mean for all 337 patients=\$4, median=\$0).

To estimate the costs of medical services, a range of medical reimbursements was used (\$50–\$75 per physician visit, \$25–\$85 for each lab test, and \$200–\$500 for each ED visit). No hospitalizations due to SSRI adverse events were recorded. Thirty-six patients had added medical costs due to side effects. Low estimates of cost ranged from \$50 for a physician visit to \$200 for an ED visit. The estimated total cost for these medical visits was \$2,350 (mean for these 36 patients=\$65, median=\$50; mean for all 337 patients=\$7, median=\$0). High estimates of cost ranged from \$75 for a physician visit to \$500 for an ED visit. The estimated total cost for these medical visits was \$4,410 (mean for these 36 patients=\$122, median=\$75; mean for all 337 patients=\$13, median=\$0).

The total direct medical cost (medications and services combined) associated with the treatment of SSRI adverse events for the 337 patients was estimated at \$11–\$17 per patient for this six-month follow-up period, with no significant differences between index drugs. Although this translates to less than \$3 per member per month, most of the costs occurred within the first one or two months of therapy.

Discussion

Assumptions and Limitations

A major assumption is that the prescription and medical records data were complete and accurate. Prescription utilization tends to be accurate because these data are collected for billing purposes. Medical records data may not be as complete because the type of information included in the medical record is left to each practitioner's discretion. The researchers only recorded adverse events if the physician's notes in the electronic medical records attributed them to the SSRI. It is possible that these adverse events may have resulted from other factors, such as other treatments or as a symptom of depression itself. Although SWHP

represents a common type of health plan, results of this study may not extrapolate to other settings with different practice patterns or formulary restrictions.

Few patients started on the index drug paroxetine. This was not considered first-line therapy at SWHP, and may have been reserved for patients who had failed other therapies. Because of the low cell sizes and the non-normality of cost data, ANOVA results should be interpreted with caution.

More than two-thirds of the patients included in the sample were female; their average age was 50 years old. Over 40% had at least one side effect due to an SSRI recorded in their electronic medical record. The most common complaints were related to sleep (insomnia or drowsiness), gastrointestinal disturbances (diarrhea, nausea), and physical/mental functioning (fatigue, low mental alertness).

The incidence of some specific adverse events (i.e., nausea and sexual dysfunction) was lower than found in the literature. The difference is probably due to the data collection methods. The cited literature used data collected from clinical trials, which specifically require patients to record all adverse events. The method used in this study only captured adverse events that were reported by the patient and recorded by the physician in the medical record. In everyday practice, some patients may not report all of the adverse events they experience, and some physicians may not record every complaint in the patient's medical record.

Almost 30% of the patients had at least one change to their drug therapy due to adverse events during the six-month observation period. About 10% had another medication added, 9% were switched to another antidepressant, and 8% discontinued the use of any antidepressant. Forty-one additional medical services were recorded as being used to treat adverse events of

SSRI use. The most common medical service was a physician office visit to change therapy. Six lab tests were ordered and three ED visits resulted from adverse events related to SSRI use; no hospitalizations were recorded.

While many patients had a change in drug therapy, the average direct medical costs to SWHP associated with the changes were relatively low (less than \$4). The average costs of other medical (nondrug) services used to treat adverse events ranged from about \$7–\$13, bringing the total direct medical costs to an average of about \$11–\$17.

Conclusion

Although 40% of patients noted at least one adverse event due to SSRI treatment, the direct medical costs to SWHP associated with the adverse events were relatively low. This cost is an underestimation of total costs; indirect costs (decrease in patient's productivity) and intangible costs (pain and suffering) were not included because, for this project, their measurement was not feasible. Future studies might investigate the additional measurement of indirect and intangible costs of these adverse events.

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