Comparison of Managed Care Charges Among Patients Treated With Selective Serotonin Reuptake Inhibitors for Premenstrual Dysphoric Disorder

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Objective: To determine the impact on managed care charges of selecting citalopram, fluoxetine, paroxetine, or sertraline as first-line pharmacotherapy for newly diagnosed premenstrual dysphoric disorder (PMDD).

Method: This retrospective study analyzed administrative claims data from 14 managed care plans in the United States. The study population was identified from an integrated outcomes database for the period Jan. 1, 1998, to Dec. 31, 1999. Patients aged 18 years or older, newly diagnosed with PMDD, and initiating therapy with a selective serotonin reuptake inhibitor (SSRI) within 30 days of the diagnosis were eligible for analysis. To date, there is no specific ICD-9 diagnosis code for PMDD; thus, patients were required to have an ICD-9 diagnosis of premenstrual tension syndrome (ICD-9 625.4). Patients with documented previous psychiatric disorders/treatment were excluded. All inpatient, outpatient, and pharmacy claims incurred by each patient during the study period were included in the analysis. PMDD-related treatment charges for the 6-month period following treatment initiation were compared using multivariate regression.

Results: A total of 1413 patients met the study criteria. Fluoxetine and sertraline were the most common agents selected as first-line therapy. After differences in age, managed care plan, pretreatment resource utilization, physician specialty, index prescription year, treatment charges, presence of mental health and nonmental health comorbid conditions, and changes in medication were controlled for, patients taking paroxetine and citalopram had significantly higher PMDD-related treatment charges than sertraline patients (paroxetine, p = .0430; citalopram, p = .0226). Fluoxetine patients also had higher treatment charges than sertraline patients, though statistical significance was not reached.

Conclusions: Sertraline, as first-line therapy for PMDD, was associated with lower PMDD-related treatment charges compared with other SSRIs during the first 6 months after treatment initiation.

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Premenstrual syndrome (PMS) is defined as emotional, behavioral, and physical symptoms that occur in the premenstrual (luteal) phase of the menstrual cycle, with resolution after menses.[1] Premenstrual complaints and PMS are common in gynecological, general medical, and psychiatric practices and are estimated to occur in up to 80% of women. Although the physical symptoms of breast pain and bloating are common, psychological symptoms of depressed mood, anxiety, and mood swings are among the most prevalent and intense complaints.[2]

Psychological symptoms, which are included in the criteria for premenstrual dysphoric disorder (PMDD), occur at a clinical level of severity in 3% to 5% of menstruating women.[2–5] While these symptoms are often voiced by patients, what is often neglected by health practitioners is the fact that premenstrual symptoms of this severity have a substantial impact on various aspects of a woman's life, such as interpersonal relationships and work performance.[2]

The therapeutic efficacy of a variety of pharmacologic treatments, including hormones, vitamins, diuretics, and psychotropic medications, has been examined.[2] Placebo-controlled studies using either progesterone or oral contraceptives suggest that these agents are no more effective than placebo with respect to psychological symptoms.[6,7] Studies of diuretics and vitamins reported mixed results; however, many of these studies suffered from methodological failings or included women with mild illness.[2]

Investigators have identified a role of serotonin (5-HT) function in many of the symptoms commonly experienced by women with PMDD, including alterations in mood, appetite, sleep, sexual interest, and impulsivity.[8] In

addition, although therapeutic inconsistencies have been demonstrated, serotonergic agents such as clomipramine, buspirone, fluoxetine, and sertraline have been efficacious in alleviating PMDD symptoms in clinical trials, suggesting a possible role of serotonin system dysregulation in PMDD.[2,8] In contrast, noradrenergic agents, such as desipramine, have not been found to be efficacious in comparison with serotonergic agents in alleviating such symptoms.[9]

Although several antidepressants have been shown to be effective for PMDD symptoms, the lower side effect profile and efficacy data for the selective serotonin reuptake inhibitors (SSRIs) support their use over other classes of antidepressants.[10] There are randomized, double-blind, placebo-controlled studies suggesting that fluoxetine, paroxetine, and sertraline may be effective at treating patients with PMDD, however, only sertraline and fluoxetine are approved by the U.S. Food and Drug Administration (FDA) for the treatment of PMDD.[2,8,9,11–13] Both sertraline and fluoxetine may be used daily or during the luteal phase of a woman's cycle. A recent meta-analysis of published clinical trials found SSRIs to be effective in treating both physical and behavioral symptoms of PMDD.[14]

To date, no head-to-head comparisons of SSRIs for treatment of PMDD have been published, and only 1 study[15] has been published exploring the use of citalopram in the treatment of this condition. Furthermore, while randomized, placebo-controlled clinical trials provide useful information on the efficacy of these agents, little is known concerning their effectiveness in actual practice or their impact on PMDD symptoms over a long time period. Therefore, the purpose of this analysis was to compare the impact of SSRI selection on resource utilization during the first 6 months after treatment initiation for PMDD. To measure resource utilization under actual practice conditions, retrospective claims data were used for this analysis. All inpatient, outpatient, and pharmacy claims incurred by each patient during the study period were included. Clinical data were not available; however, resource utilization is considered a useful measure of treatment effectiveness and can help to discern differences in outcomes of treatment selection.[16–18]

METHOD

Description of Database

Patient-level clinical and cost data were captured from a retrospective analysis using a proprietary database developed by PharMetrics (Watertown, Mass.). The PharMetrics Integrated Outcomes Database contains over 100 million episode-of-care linked medical and pharmaceutical claims constructed using state-of-the-art database technology. The database contains patient- and disease-specific episodes of care, which reflect a longitudinal picture of the resources consumed by continuously enrolled member populations. The database includes patient-level medical and pharmaceutical claims representing over 16 million managed care subscribers across the United States.

Patient Identification

The study population was identified from the database using *International Classification of Diseases, Ninth Revision* (ICD-9) codes for the period Jan. 1, 1998, to Dec. 31, 1999. Subjects were required to have a primary diagnosis of premenstrual tension syndrome (ICD-9 625.4) and to have initiated therapy with an SSRI (citalopram, fluoxetine, paroxetine, sertraline) within 30 days of the index diagnosis. To date, there is no specific ICD-9 code for PMDD. It was felt, however, that patients with a claim for ICD-9 code 625.4 (primary diagnosis of premenstrual tension syndrome) who were treated with an SSRI could be considered to have PMDD, as the less severe illness categorized under this code (i.e., PMS) is not typically treated with an SSRI. Therefore, ICD-9 code 625.4 was the most appropriate code to use for patients with PMDD. Patients diagnosed with other mental health conditions within the 6 months prior to the initial PMDD-related claim were excluded from the analysis. Excluded conditions included depression (ICD-9 296.2, 296.3, 300.4, 311), anxiety disorder (ICD-9 300), and posttraumatic stress disorder (ICD-9 309.81).

Patients receiving prescriptions related to the treatment of PMDD or other psychiatric conditions (i.e., SSRIs, tricyclic antidepressants [TCAs], benzodiazepines, mirtazapine, trazodone/nefazodone, venlafaxine) within the 6-month period prior to initial diagnosis were excluded, as were subjects less than 18 years of age at the index diagnosis. Subjects were also excluded if they possessed diagnoses indicative of bipolar disorder (ICD-9 296.0, 296.1, 296.4–296.9) or schizophrenia (ICD-9 295.xx).

To ensure adequate capture of all treatment/utilization, study participants were required to have been continuously enrolled in their respective health plans for at least 6 months prior to and 6 months following their initial SSRI prescription claim.

Study Variables

The primary outcome of interest in this study was PMDD-related treatment charges for the 6 months after therapy initiation. Disease-specific treatment charges were classified as inpatient (i.e., all claims for care occurring in a hospital setting), outpatient (i.e., physician visits), ancillary (lab tests, other nonphysician claims), emergency room (ER), and pharmacy, as indicated by the type of claim submitted for reimbursement. Thus, the analyses allowed for the consideration of costs from a payer's perspective. PMDD-related medical charges were calculated

using all medical claims with a primary diagnosis of premenstrual tension syndrome and pharmacy claims after the diagnosis for SSRIs, TCAs, benzodiazepines, mirtazapine, trazodone/nefazodone, and venlafaxine.

Patient demographic information (i.e., age, region), physician specialty associated with the initial PMDD-related medical claim, presence of comorbid conditions, and use of other medications in the follow-up period were included in multivariate analysis, since these variables may distort the relationship between the main effect variable and the outcome of interest.

Analysis

Descriptive measures and treatment outcomes were compared across treatment cohorts. Tests of significance were conducted on continuous variables using t tests; tests on categorical variables utilized tests of proportions. An a priori significance level of $p = .05$ was chosen for all significance tests. All analyses were conducted using SAS Version 8.1 (SAS Institute, Cary, N.C., 2001). For the multivariate regression analysis, PMDD-related treatment charges were natural log-transformed to address any heteroskedasticity associated with the distribution of the observed results.

Adjusting for Differences in Baseline Characteristics

The retrospective and nonrandom nature of the data allowed for potential selection bias in the selection of the initial SSRI. For example, physicians may select a newer agent, or one perceived as more effective, for more severely ill patients and reserve older agents, or agents perceived as less effective, for patients with fewer symptoms or less severe illness. If this were not taken into account, the analysis would be biased against the agent being preferentially prescribed to the sicker patients.[16] While all efforts were made to remove channeling bias through the exclusion of patients with prior diagnosis/treatment, differences in disease severity may have existed across the treatment cohorts. Although it was not possible to measure disease severity directly, a number of secondary measures were collected and included as covariates in a multivariate regression model. These secondary measures included total medical charges for the 6 months prior to the index date, the utilization of ER or hospital care prior to the index date, and the number of other diagnosed conditions present at baseline. While not direct measures of disease severity, the secondary measures do indicate resource utilization prior to the point when pharmacotherapy was initiated; such utilization may be correlated to disease severity.[19]

Similarly, if a managed care plan has a prior authorization program, the newer agent may only be prescribed to sicker patients, or at least to those who have received other treatment and have not responded. To address these potential biases, multivariate regression analysis was used to compare disease-related treatment charges across the cohorts, after controlling for the following variables: patient age, the natural log of pre–study period treatment charges, presence of mental health and nonmental health comorbid conditions, the patients' managed care plans, the physician specialty associated with the index diagnosis indicative of PMDD, utilization of ER or hospital services in the 6 months prior to the index PMDD-related medical claim, and the year of the initial diagnosis (1998 vs. 1999). As mentioned previously, comorbid diagnoses and prior utilization are commonly used indicators of disease severity and are generally strong predictors of future utilization. Physician specialty was utilized as a covariate to account for differences in disease severity for patients treated by specialists versus generalists. The managed care plan variable was included to control for regional and plan-specific differences in medical charges and/or treatment patterns, while the year of initial diagnosis was included to account for any changes in treatment patterns that may have occurred over time.

As the dependent variable (PMDD-related treatment charges) was natural-log transformed prior to the multivariate regression analysis, beta coefficients for each variable in the model are interpreted as "percentage change" (i.e., if the beta coefficient for male gender is 0.16, this corresponds to a 16% difference in charges between men and women).

RESULTS

A total of 1413 patients met all inclusion/exclusion criteria and were included in the study sample. Fluoxetine (N = 532, 38%) and sertraline (N = 519, 37%) represented the 2 most commonly prescribed SSRIs in this cohort. Only 6% of the patients in this dataset received citalopram, the newest agent in this study. Sample demographics are presented in Table 1. On the whole, the cohorts were similar; however, there were some notable exceptions. Citalopram patients were significantly more likely to have received their initial diagnosis in 1999 rather than 1998 (70%, $p < .001$) compared with the other treatment cohorts. Sertraline patients, while similar to fluoxetine patients in all other aspects, were significantly less likely to have been diagnosed by a psychiatrist (9% vs. 14%, $p = .0198$).

As shown in Table 1, PMDD-related treatment charges were approximately $165 for the 6-month study period. Sertraline patients incurred $126 per patient in PMDD-related charges. This amount was significantly less than the mean charge for paroxetine ($p = .02$) and nonsignificant versus fluoxetine ($p = .20$) and citalopram ($p = .50$). Sertraline patients also incurred the lowest total (any reason) charges (mean = $1649) for the study period compared with $1828 and $1892 for paroxetine and fluoxetine,

Table 1. Sample Demographics and Mean Treatment Charges for PMDD Patients Treated With an SSRI

Variable	Citalopram (N = 86)	Fluoxetine (N = 532)	Paroxetine (N = 276)	Sertraline (N = 519)
Age, mean (SD), y	36.0 (8.4)	38.0 (7.1)	37.4 (7.5)	36.9 (7.0)
Physician specialty, N (%)				
General practice	18 (20.9)	177 (33.3)	110 (39.8)	196 (37.8)
Psychiatrist	16 (18.6)	75 (14.1)*	32 (11.6)	49 (9.4)
Other	52 (60.5)	280 (52.6)	134 (48.6)	274 (52.8)
Index year, N (%)				
1998	26 (30.2)	274 (51.5)	140 (50.7)	268 (51.6)
1999	60 (69.8)†	258 (48.5)	136 (49.3)	251 (48.4)
Comorbid conditions, N (%)				
Migraine	3 (3.5)	13 (2.4)	6 (2.2)	15 (2.9)
Hypertension	2 (2.3)	12 (2.3)	5 (1.8)	9 (1.7)
Epilepsy	1 (1.2)	2 (0.4)	1 (0.4)	0 (0)
Substance abuse	0 (0)	3 (0.6)	2 (0.7)	3 (0.6)
Diabetes	1 (1.2)	1 (0.2)	3 (1.1)	1 (0.2)
Treatment charges, mean (SD)				
PMDD-specific	$158 (346)	$160 (451)	$217‡ (775)	$126 (336)
Any reason	$4980 (31,141)	$1892 (3328)	$1828 (2722)	$1649 (2727)

*p = .0198 vs. sertraline.
†p < .001 vs. other cohorts.
‡p = .022 vs. sertraline.
Abbreviations: PMDD = premenstrual dysphoric disorder, SSRI = selective serotonin reuptake inhibitor.

Table 2. Multivariate Regression of PMDD-Related Treatment Charges[a,b]

Variable	Reference	Beta Coefficient	Standard Error	p Value
Citalopram	Sertraline	0.56	0.24	.0226
Fluoxetine	Sertraline	0.16	0.13	.2131
Paroxetine	Sertraline	0.31	0.15	.0430
Switched medication	No switch	0.46	0.22	.0157
Added medication	No addition	0.37	0.33	.1474
Hospitalized in preperiod	No hospitalization	3.52	0.79	.0103
ER use in preperiod	No ER use	1.56	0.59	.0242
Diagnosed by general practitioner	Diagnosed by psychiatrist	–1.52	0.74	.0424
Diagnosed by other physician specialty	Diagnosed by psychiatrist	–1.84	0.74	.0136
1 comorbid diagnosis[c]	No comorbid diagnoses	3.99	0.16	.0001
2 comorbid diagnoses[c]	No comorbid diagnoses	4.90	0.31	.0001
3 comorbid diagnoses[c]	No comorbid diagnoses	3.70	1.60	.0207
Age 19+ y	Age < 19 y	0.07	0.76	.9238
Preperiod charges	Unit increase	0.000013	0.000018	.4673
Diagnosis in 1998	Diagnosis in 1999	0.083	0.091	.3612

[a]Also controlled for managed care plan (14 plans included in analysis).
[b]Model information: $R^2 = 0.4402$, adjusted $R^2 = 0.4276$.
[c]Comorbid diagnoses = attention-deficit/hyperactivity disorder, coronary artery disease, diabetes, epilepsy, hypertension, hyperlipidemia, migraine, osteoarthritis, rheumatoid arthritis, sexual dysfunction, substance abuse.
Abbreviations: ER = emergency room, PMDD = premenstrual dysphoric disorder.

respectively. Although patients treated with citalopram had the highest mean total (any reason) charges over the study period ($4980), the large standard deviation (31,141) makes meaningful comparison of these charges with those in the other groups problematic.

Multivariate analyses, which adjusted for differences across the treatment cohorts, found similar results. As shown in Table 2, patients initially prescribed sertraline for the treatment of PMDD incurred 56% lower PMDD-related treatment charges than patients initially prescribed citalopram (p = .0226) and 31% lower treatment charges than patients receiving paroxetine (p = .0430) after differences in baseline characteristics, including pretreatment charges, were controlled for. Again, sertraline patients, on average, had numerically lower PMDD charges than fluoxetine patients (16%); however, statistical significance was not achieved (p = .2131). The multivariate model explained approximately 43% of the variation in PMDD-related treatment charges, which is consistent with other regression analyses of disease-related costs.[16,17] Other factors found to be statistically significant regarding PMDD-related treatment charges included pre–study period charges, presence of comorbid medical conditions, patient age, change in medication type, managed care plan, physician specialty, and year of diagnosis (Table 2).

DISCUSSION

A MEDLINE search found no head-to-head comparison of SSRIs in the treatment of PMDD. While numerous pharmacoeconomic analyses have focused on SSRI use in depression, anxiety, and other mental health conditions, research in PMDD has been limited to clinical trials that have usually compared the study product to a placebo, and most have followed patients for only a short time.[2,8,12] A recent meta-analysis of several clinical trials found SSRIs to be an effective first-line therapy for PMDD, based on their side-effect profile and impact on both physical and behavioral symptoms.[14] Notably, the conclusions of these trials about long-term safety and efficacy were based on studies in affective disorders, since there was no information that limited long-term use of SSRIs in PMDD at the time the article was written.[14]

Mean PMDD-related treatment charges ranged from $126 to $217 per patient for the 6-month study period. This may be an underestimate of true PMDD-related treatment charges if medication was prescribed during a physician visit for another complaint or if miscoding of the reason for the visit occurred. However, by analyzing both PMDD-related and total treatment charges, the effect of any miscoding can be minimized. Total (all causes) charges for this sample were over 10 times this amount, ranging from $1649–$4980 per patient, highlighting the significant financial cost of patients with this condition.

In this analysis, initial treatment of PMDD with sertraline, compared with the other SSRIs, appeared to be associated with lower PMDD-specific and total treatment charges. PMDD-related charges initially appear to be quite low; however, other than the medication costs, many of the PMDD-related charges may be coded for other reasons. For example, if a patient goes to her physician for another reason, but while in the office is prescribed medication for PMDD, the primary reason for the visit would not be coded as premenstrual tension disorder. Alternatively, when a patient presents with multiple complaints, reimbursement requirements may influence the order in which diagnoses are coded. While treatment charges are not necessarily indicative of symptom severity or alleviation, it is logical to assume that patients who are not receiving adequate response from their initial treatment will continue to seek medical care and hence incur more cost.

After differences in baseline characteristics across the study cohorts were adjusted for, patients treated with either citalopram or paroxetine, on average, incurred PMDD-related treatment charges 56% and 31% higher, respectively, than patients initially receiving sertraline despite the lower acquisition cost of citalopram. This would suggest that these differences are not due to differences in the patients who were prescribed each medication or the acquisition cost of the medications but are instead due to differences in the medications and in how patients responded to them. It is important to recognize that the FDA has not approved paroxetine or citalopram for the treatment of PMDD; therefore, further research is needed to determine their effectiveness in treating this condition.

Data for the analyses were obtained before generic fluoxetine was available. The lower acquisition cost of generic fluoxetine would most likely have a meaningful effect on the cost of PMDD-related treatment for that group. However, the use of a luteal phase dosing strategy in patients with PMDD without a comorbid anxiety disorder or depression could result in less medication usage and, consequently, meaningfully lower medication costs for patients treated with sertraline or fluoxetine.

One frequent criticism of retrospective analyses focuses on the fact that patients are not randomized to treatment groups, making it possible that underlying differences in the treatment cohorts influenced the results observed. To minimize the effect of possible differences, treatment charges were compared using multivariate regression to control for differences in baseline characteristics across the treatment cohorts. This is a widely used and effective technique; however, it is possible that variables not included in the model, such as previous treatment outside the study period, may have affected the results. However, if the unobserved variables were not correlated with variables in the model, then not including them would not have affected the magnitude of the parameter or effect estimates but merely reduced the predictive power of the model. Similarly, any errors in the data, such as coding omissions that were randomly distributed as opposed to being confined to 1 treatment group, would not be expected to lead to biases in the parameter or effect estimates.

A number of surrogate measures for disease severity were included as covariates in the regression model of PMDD-related treatment charges. While it was not possible to ascertain the correlation of these variables with respect to clinical severity, they were statistically significant predictors of higher PMDD costs in the post–study period, supporting their use for severity adjustment. For example, patients who visited the ER in the pre–study period incurred significantly higher charges in the post–study period versus those that did not, as did patients treated by a psychiatrist versus those treated by a generalist or other physician specialty.

Treatment charges were the primary outcome of the analysis. Since symptom severity was not measurable in these data, it is not possible to determine if differences in treatment charges were due to superior efficacy or some other characteristic of sertraline compared with the other SSRIs. That being said, the differences in treatment-related charges between groups suggest that there may be important differences between these agents with respect to their effect on resource utilization when used to treat patients with PMDD. The use of charge data to

estimate cost may have artificially inflated the true cost of treatment. The use of standard cost-to-charge ratios or other methods for converting charges to cost were not employed in this analysis, given the lack of uniform consensus on an appropriate ratio or method for such conversions. Furthermore, any conversion would need to be employed equally across all study patients so the direction/magnitude of the observed differences between groups should not change.

Unfortunately, PMDD is not specifically identified within the ICD-9. For this analysis, it was assumed that any woman receiving a diagnosis indicative of premenstrual tension syndrome (ICD-9 625.4) and receiving treatment with an SSRI had PMDD, based on the supposition that SSRI treatment would be reserved for only those women with more severe illness (which would in turn qualify them for PMDD). It is possible that some study patients were misclassified as having PMDD that did not, which may have impacted the results; however, there is no evidence to suggest that this misclassification would have been systematic such that the study cohorts would have been nonequally affected.

In the past decade, there has been a rapid expansion in the amount of information available about PMS and, more specifically, PMDD.[1,3] SSRIs have shown the most promise in alleviating PMDD-related symptoms. There are many factors to consider when selecting an SSRI for the treatment of PMDD, including the patient's symptoms, the proven efficacy of the medication in treating those symptoms, the tolerability of the agent, and the practitioner's experience with that agent. Cost is also an important consideration in making treatment choices; however, choosing an agent with a low acquisition cost without consideration of the total cost of treatment will most likely result in a false economy. The results presented here suggest that sertraline may be associated with the lowest PMDD-related treatment costs for patients with PMDD.

Drug names: buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), escitalopram (Lexapro), fluoxetine (Sarafem and others), mirtazapine (Remeron and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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