Over the past 15 years, significant advances have occurred in the pharmacotherapy of depression. Previous first-line antidepressants such as tricyclic antidepressants (TCAs) have been largely replaced by selective serotonin reuptake inhibitors (SSRIs) and other newer medications. In particular, the SSRIs have become popular because of more tolerable side effects, greater safety in overdose, and ease in dosing and administration.

People experiencing depression who do not receive adequate antidepressant treatment are more likely to have high rates of concurrent medical disorders, are less productive in the workplace, and utilize more health care resources than non-depressed people. Those who tolerate medications and comply with their antidepressant medication regimens for a full course of therapy are more likely to achieve positive clinical outcomes, leading to improved quality of life and cost avoidance for both additional outpatient and inpatient psychiatric care. The majority of antidepressant medications dispensed in the United States are SSRIs. Within the Texas Medicaid program, SSRIs accounted for 52% of all antidepressants dispensed to clients in 2000. Due to their higher unit costs, compared to older agents, these newer generation agents accounted for 71% of all antidepressant costs over the same year.

While SSRIs may cost more in direct drug cost compared to older antidepressants, multiple outcomes studies show that SSRIs are as efficacious as the traditional medications and are better tolerated by patients, indicating clinical and economic benefits for the medication costs expended. Only one administrative database study has been published comparing both pharmacy and health service utilization and costs associated with citalopram use. Results of the study, conducted by Sclar et al. in a health maintenance organization, showed that amitriptyline and sertraline were associated with higher health service utilization costs than citalopram, and there were no significant differences in costs among citalopram, fluoxetine, and paroxetine. However, since the study period shortly followed the market release of citalopram, a relatively small sample size within the citalopram group was used for the comparisons.

As the use of SSRIs continues to increase within the Texas Medicaid Program, total expenditures for this drug class will similarly continue to increase. Because the economic impact of this particular class of drugs is significant within the program, an analysis of the growing impact was undertaken. The objective of this paper is to evaluate trends in the use of selected SSRI agents and venlafaxine and their associated pharmaceutical expenditures within the Texas Medicaid Vendor Drug Program during 1999 and 2000.
Methods

All paid prescription drug claims were extracted from the Texas Medicaid Vendor Drug Program’s paid prescription claims database for the study period of January 1, 1999, to December 31, 2000. Clients aged 18 to 64 years were included in the study if they had at least one prescription dispensed for one of the selected study agents (citalopram, fluoxetine, sertraline, paroxetine, venlafaxine, and venlafaxine XR) at any time during the study period. Although venlafaxine is not strictly an SSRI at higher doses, it is included in this study because it is a newer antidepressant that is frequently used in primary care as well as psychiatric settings.

Utilization and Expenditure Measurements

Mean Reimbursed Cost per Day

Cost per day was calculated by dividing the pharmacy-reimbursed prescription payment (drug cost plus dispensing fee) by the number of days found in the “days supply” field within the prescription record. This “days supply” value is submitted by the pharmacy during the claims adjudication process and represents the number of treatment days for the dispensed quantity, based upon the therapy regimen prescribed by the physician. Reimbursed amounts represent the actual amount paid to the pharmacies and do not include rebates paid to the Texas Medicaid program on behalf of drug manufacturers, as mandated under OBRA ’90 requirements. The pharmacy payment amount excludes copayments since there are no Medicaid recipient copayments in Texas. The cost per day reported in this study is equivalent to the allowed cost per day in private drug plans, before member copayment, which includes the effects of “lowest-of” pricing (i.e., the lower of usual and customary price or the contract price calculated as the drug cost plus dispensing fee).

Mean Dose per Day

For each study agent prescription dispensed, a daily dose was calculated by multiplying the quantity dispensed by the drug strength, then dividing by the days supply field within the prescription record. Prescription claims were grouped by study agent and actual dispensing date to allow for situations where the use of different strengths of the same drug were dispensed on the same day. For each patient, the following measures were calculated: (1) mean starting dose, (2) mean maximum dose, and (3) percent of patients with a dose increase during treatment.

Mean Length of Treatment (Persistence)

Length of treatment provided a measure of the persistency of prescription use and was calculated by summing the number of days between the start and end date of the treatment window for the study agent. The start date was defined as the first date of dispensing of the study agent with no previous dispensing 120 days prior to the first prescription for the study agent. This inclusion criterion served as a proxy for defining newly started patients, i.e., treatment of a new episode of illness. Subsequent prescriptions were included as part of the treatment duration if a prescription was dispensed within 15 days of the end date of the previous prescription. The end date was calculated for each prescription by adding the number of days found in the days supply field to the dispensing date. This created the “treatment window” for each prescription. If no subsequent prescription was dispensed within 15 days of the previous prescription, then the end date for the last prescription constituted the last day of treatment and, thus, the end of the treatment window.

Adherence Rates

Adherence (compliance) rates were compared by calculating days of medication possession for the first 120 days of therapy for newly started patients. New starters were defined, as described earlier, as clients having no previous prescription dispensed for any study agent for 120 days prior to the first appearance of a claim for the study agent. The date of the first claim served as an index date. Total days supply were summed for all dispensed prescriptions during the first 120 days following the index date. Any occurrence of overlapping days supply was corrected by subtracting the total overlapped days from the total days supply calculated. Days of therapy that carried over past the 120th day of therapy were subtracted from the total days supply calculated. Newly started patients were selected, as opposed to ongoing patients, in order to measure medication possession across a well-defined period of time that included a definitive starting date.

Concomitant Psychotropic Medication Use

McFarland notes that the costs associated with concomitant drug use should be considered when comparing the economic impact of antidepressant agents. Therefore, the cost of these agents was considered in our comparisons. Patients included in the calculation of mean treatment days were also included in an analysis to measure the frequency and additional costs associated with concomitant psychotropic medication use. Concomitant agents were identified based on the utilization of any sedative, hypnotic, anxiolytic, or psychostimulant agent while concurrently taking one of the study agents. Concomitant medication use was defined as the dispensing of the concomitant medication between the start and end date of either study agent during the client’s treatment course of therapy. All available strengths of each concomitant agent were included in the analysis. Total costs of all concomitant agents were summed for each patient and divided by the study agent treatment days to calculate a concomitant agent cost per day.

Rates of Switching

Patients were defined to have “switched” therapy if, at any time during the study period, the patient received one prescription for a study agent, then received a subsequent prescription for the other study agent within 30 days of the end of the previous prescription end date (defined earlier as the dispensing date plus the days supply of the prescription). For example, if a

Economic Evaluation of Citalopram Use and Expenditures Among Recipients in the Texas Medicaid Program
patient received a prescription for citalopram on January 1, 1999, for a 30-day supply of medication, then received a subsequent prescription for fluoxetine at any time between January 1, 1999, and March 2, 1999, a product switch was deemed to have occurred. Both the number of switches for each agent and the percent of switched patients as a percent of the total number of patients were calculated.

Statistical Analyses
Statistical comparisons between study groups were conducted using chi-square analyses to determine differences in gender classification between groups. Comparisons between the mean values of each selected dependent variable were conducted using analysis of variance, using the study group as the independent variable. In cases where the dependent variable distribution was not normal, a Wilcoxon signed rank test was conducted to compare differences between groups. A significance level of 0.001 was selected, due to the large sample sizes within each study group.

Results

Study Population Description
Table 1 describes the patient populations included in the study based upon (1) number of prescriptions, (2) days of therapy, (3) number of patients, (4) percent females, and (5) mean age.

Mean Study Agent Dose
In all study groups, except venlafaxine, the mean maximum dose per patient was significantly higher than the mean starting dose per patient (Wilcoxon signed rank test versus mean starting dose, P<0.001). There was no difference between citalopram and all other agents (except venlafaxine, chi-square versus citalopram, P<0.001) with respect to the percent of patients having an increase from their initial starting dose over the course of the treatment period. However, the incidence of dose increases was extremely low with all medications (citalopram 9.9%, fluoxetine 8.1%, paroxetine 9%, sertraline 10.2%, venlafaxine IR 5.3%, and venlafaxine XR 12.7%).

Length of Treatment Days (Persistence)
Table 2 shows that the mean treatment days for newly started citalopram patients was 83.2 days. There was no significant difference in mean treatment days between citalopram and all

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>1999</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rxs</td>
<td>Days of Therapy</td>
</tr>
<tr>
<td>Citalopram</td>
<td>15,369</td>
<td>584,632</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>58,210</td>
<td>2,203,139</td>
</tr>
<tr>
<td>Sertraline</td>
<td>62,458</td>
<td>2,416,470</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>51,735</td>
<td>1,927,512</td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>7,922</td>
<td>280,768</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>17,840</td>
<td>667,052</td>
</tr>
</tbody>
</table>

* Chi-square versus citalopram, P<0.001.
† ANOVA versus citalopram, P<0.001.
‡ ANOVA versus citalopram, P<0.001.

Economic Evaluation of Citalopram Use and Expenditures Among Recipients in the Texas Medicaid Program

Table 1.

Texas Medicaid SSRI Patients Summary and Cost-per-Day Comparison

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>1999</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rxs</td>
<td>Days of Therapy</td>
</tr>
<tr>
<td>Citalopram</td>
<td>15,369</td>
<td>584,632</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>58,210</td>
<td>2,203,139</td>
</tr>
<tr>
<td>Sertraline</td>
<td>62,458</td>
<td>2,416,470</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>51,735</td>
<td>1,927,512</td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>7,922</td>
<td>280,768</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>17,840</td>
<td>667,052</td>
</tr>
</tbody>
</table>
other study agent patients, except venlafaxine patients, who had significantly lower mean treatment days (66.0 days). Additionally, a comparison of the percent of patients receiving at least 120 days of continuous treatment, significantly less than fluoxetine (48.3%) and significantly more than venlafaxine (29.1%).

Adherence Rates
Total days of medication during the first 120 days of therapy for all newly started study agent patients were summed to determine the rate of adherence across agent patient groups (Table 3). Newly started citalopram patients had significantly higher mean days of adherence (69.4 days) during the first 120 days of therapy, compared to all other study agents except fluoxetine (68.5 days). Patients newly started on venlafaxine had the lowest calculated adherence rates of all study agents (55.1 days). The calculated adherence rate for citalopram was 57.8%, followed by fluoxetine (57.1%, \(P=0.478\)), sertraline (55.4%, \(P<0.001\)), venlafaxine XR (55.3%, \(P<0.001\)), paroxetine (53.2%, \(P<0.001\)), and venlafaxine (45.9%, \(P<0.001\)). While these differences are statistically significant, the clinical significance of these differences should be considered here where the differences are mostly 2 to 3 total days between agent groups with large sample sizes.

Rates of Agent Switching
Table 4 shows the rates of switching for newly started SSRI patients within 180 days of starting the initial study agent. The majority of newly started patients did not switch agents during the first 180 days of SSRI therapy. A total of 13.4% of citalopram patients switched to another study agent, and similar rates were calculated for patients starting on sertraline (10.6%), fluoxetine (12.0%), and paroxetine (12.9%). Compared to all other study agents, venlafaxine (34.7%) and venlafaxine XR (20.9%) had larger rates of switching between agents; however, the majority of the switching was between the immediate and sustained-release tablets.

The mean number of days to the first switch for newly started study agents that were actually switched was calculated and is shown in Table 4. Patients started on citalopram who switched to another study agent did so, on average, after 83.5 days of starting the agent. There was no significant difference between citalopram and all other study agents, except venlafaxine (70.9 days).

Concomitant Medication Use
The prevalence and expenditures related to concomitant medication use for each study agent are shown in Table 5. Among newly started patients, citalopram had a slightly higher rate of concomitant medication use (46.1%) during treatment days on the study agent compared to patients started on fluoxetine (39.7%), sertraline (38.6%), paroxetine (42.8%), and venlafaxine (45.7%). Of the study agents, only venlafaxine XR had a higher rate of concomitant use (47.6%), compared to citalopram.

Mean CPD of concomitant agents used during treatment

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>N</th>
<th>Mean Treatment Days</th>
<th>% of Patients With 120 Days or More</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>3,575</td>
<td>83.2 (99.6)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>6,590</td>
<td>85.5 (103.5)</td>
<td>0.883</td>
</tr>
<tr>
<td>Sertraline</td>
<td>8,905</td>
<td>83.8 (103.5)</td>
<td>0.999</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>7,961</td>
<td>79.0 (99.1)</td>
<td>0.312</td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>979</td>
<td>66.0 (84.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>2,535</td>
<td>80.6 (96.4)</td>
<td>0.929</td>
</tr>
</tbody>
</table>

* Chi-square versus citalopram, \(P<0.001\).

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>N</th>
<th>Mean Adherent Days (Out of 120)</th>
<th>Adherence Rate</th>
<th>% of Patients With 120 Days or More</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>4,432</td>
<td>69.4 (34.3)</td>
<td>57.8%</td>
<td>n/a</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>8,208</td>
<td>68.5 (33.8)</td>
<td>57.1%</td>
<td>&lt;0.478</td>
</tr>
<tr>
<td>Sertraline</td>
<td>10,084</td>
<td>66.5 (33.9)</td>
<td>55.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>8,943</td>
<td>63.8 (33.5)</td>
<td>53.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venlafaxine IR</td>
<td>1,482</td>
<td>55.1 (32.3)</td>
<td>45.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>3,707</td>
<td>66.3 (33.9)</td>
<td>55.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
days for newly started patients is shown in Table 5. Patients started on citalopram had additional mean daily prescription costs of $0.19 related to concomitant agent use. Patients started on sertraline had a significantly lower mean CPD for concomitant agents ($0.14), compared to citalopram ($0.19, P<0.001). There was no significant difference in mean CPD of concomitant agents between citalopram and any other study agent.

### Discussion

Retrospective prescription claims databases are useful in describing prescription utilization and expenditure trends within drug benefit programs. In the case of SSRI prescribing within the Texas Medicaid Program, our analyses showed that the use of these newer generation antidepressant agents continues to increase, both in the number of prescriptions dispensed and the number of patients treated. The use of citalopram within the Texas Medicaid program has increased steadily over the last 2 years, outpacing the growth in prescriptions and patients treated with other SSRI agents.

In measuring the overall impact of citalopram on the Texas Medicaid program, we focused on making comparisons to other SSRI agents and venlafaxine with respect to selected measurements of utilization and expenditure trends. We first measured the difference in relative product costs for the treatment with the respective agents. We chose to compare calculated costs per day, since a comparison could be made between agents without regard to differences in days supply associated with each prescription. We found that citalopram was significantly less expensive, on a cost-per-day basis, than all other agents in 1999 and in 2000, except for venlafaxine. As a comparison, citalopram was 55% less expensive than fluoxetine during 2000 (Table 1). Mean daily costs were also significantly lower for citalopram compared to venlafaxine XR (36% lower), sertraline (14%), and paroxetine (11%). These results obviously do not reflect the advent of generic fluoxetine, which was not available at the time of this study. Cost trends need to be monitored over time as the marketplace changes secondary to generic competition.

We found that there was no significant difference between citalopram and the comparison agents, except rapid-release venlafaxine, with respect to the mean length of treatment for newly started patients (Table 2). This indicator is important because length of treatment can be affected by factors related to side effects of the medication, disease response, denial of illness, and patient adherence, in general. Sclar has used the achievement of 90 days of continuous treatment as a marker of clinical response in treating an acute depressive episode. The absence of a statistical difference between citalopram and the comparator antidepressants may be an indicator that similar treatment responses are being experienced within the Texas Medicaid Program.

Contemporary treatment guidelines for major depressive disorder typically recommend an increase in antidepressant dosage within 6 weeks if the patient is experiencing an inadequate improvement in depressive symptoms. Additionally, naturalistic studies indicate that only about 50% of depressed patients receive
a clinically significant improvement in symptoms in a real-world setting. This, combined with a dosage increase in only about 10% of patients in this study, would suggest that patients with depression are receiving inadequate treatment.

We evaluated the adherence rate that newly started patients achieve with each antidepressant agent. Poor patient adherence is a major factor affecting successful outcomes with antidepressant treatment. Studies have shown that 28% of patients drop out of treatment within the first month, 44% by the third month, and that only 20% to 34% have 4 or more prescriptions filled within 6 months of the initial prescription.17,18 Adherence, as with length of treatment (persistence), may be affected by lack of improvement in symptoms, improvement in symptoms and failure to follow through with continuing treatment, dosing schedule, side effects or adverse events associated with taking the medication, or dissatisfaction with the care being provided by a provider or organization.13,18 Patients who have higher levels of adherence will typically achieve more positive clinical outcomes than patients who are nonadherent. Thus, the low persistence and adherence rates indicated in Tables 2 and 3 are suggestive of overall inadequate treatment outcomes among this patient population. Our analysis showed that there was not a significant difference in adherence between citalopram and fluoxetine, but all other comparator agents had a significantly lower adherence rate than citalopram (Table 3). The mean adherence rate (57.8%) that we calculated for citalopram patients during the first 120 days of therapy is consistent with typical adherence rates for antidepressant therapies. Whether these stated statistical differences are clinically significant is open to debate. However, the adherence rate with rapid release venlafaxine (45.9%) appears to be clinically significantly lower than the other agents.

We evaluated the degree to which newly started SSRI patients switch from the starting drug to another SSRI within the first 180 days of therapy. This time frame is critical as 6 months of pharmacotherapy represents the minimum duration of successful treatment for an acute depressive episode (i.e., successful acute treatment plus a minimum continuation phase to prevent relapse).1,2 Early discontinuation of antidepressant treatment and switching to alternate antidepressants have been associated with increased direct medical costs.19,20 This measurement may be indicative of many factors, including symptom improvement and tolerability of the medication. In addition, product switching may increase the number of office visits for patients who are not well controlled on their initial agent, which has been shown to be associated with increased health services expenditures.20 As a general trend, across the antidepressant comparator groups, most patients did not switch to another agent (Table 4). Of the patients who were started on citalopram, 13.4% switched to a comparator agent during the first 6 months of therapy. Similar trends were seen across the other SSRI agent groups. While venlafaxine and venlafaxine XR patients had higher rates of switching than the other study agents, the majority of the switching was between the shorter- and longer-acting venlafaxine agents and not necessarily between other chemical entities. The high rate of switching from venlafaxine to venlafaxine XR might be explained either by the better tolerability of the long-acting product or the promotion of the XR form to physicians. Although these data do not address causality for a higher switch rate from venlafaxine to the sustained release product, Entsuah and Chitra, in a head-to-head comparison, found that venlafaxine XR had a significantly superior benefit-to-risk ratio of 2:1 over venlafaxine IR for the side effects of nausea and dizziness.5 Extrapolating from Sclar’s work looking at the relationship between antidepressant switching and service utilization costs, these data may indicate increased health care costs with venlafaxine and suggest that the sustained-release form should be the only form of venlafaxine on drug formularies.16 The preferential use of venlafaxine XR over the immediate-release product is also recommended in practice guidelines.1

As discussed earlier, the use of concomitant agents is important to consider when making economic comparisons between treatment agents, as their increased use will further increase the overall costs of the drug therapy regimen. We found that 46.1% of newly started citalopram patients used at least one concomitant agent during their treatment period (Table 5). This rate was slightly higher than most other study agents except venlafaxine XR. However, when comparing the additional costs related to the use of concomitant agents, we found no significant differences in the cost per day of treatment with these agents between citalopram and all other agents, except fluoxetine. In the case of fluoxetine, the difference in mean concomitant agent cost per day was approximately $0.05 per day per patient. While this difference is statistically significant, it is substantially less than the $1.30 difference per day per patient between citalopram ($2.36) and fluoxetine ($3.36) in 2000.

**Limitations**

As is common with many naturalistic studies, there are study design limitations that should be considered when making generalizations from these results. Diagnostic information and service utilization data are not available for analysis within the prescription drug claim records. The database also provides no indication of disease severity or response in symptoms or function associated with treatment. Therefore, no attempt was made to classify or control for any differences in diagnosis types or disease severity. Prescription claims included in this analysis may also represent antidepressant use for disorders other than depression. Furthermore, accurate information regarding patient eligibility periods was not available for comparison across study agent groups. While the sample sizes included in these analyses are quite robust, utilization patterns exhibited by Medicaid patients may not be generalizable to non-Medicaid populations.

Clinical trials of antidepressants in the outpatient environment have failed to find any meaningful overall differences in efficacy or
effectiveness among agents. 22,23 While studies of pharmacy claims databases do not contain information that directly reflect patient clinical outcomes or service utilization, a number of markers for this information can be used. The fact that there were no clinically meaningful differences among agents in duration of treatment, dosage increases, patient adherence, or medication switching suggests that the compared agents, with the possible exception of venlafaxine IR, are similar with regard to clinical outcomes. The switch data from venlafaxine IR to XR is consistent with reports of less tolerability with the rapid-release product. Therefore, our comparisons that identify lower costs per day for citalopram patients suggest that cost minimization may be realized with the use of citalopram within this Medicaid population.

Finally, because our analyses included available prescription claims data for the time period of 1999 to 2000, we did not include the generic version of fluoxetine in our analyses, since patent protection on brand fluoxetine was maintained through August 2001. Future studies that compare utilization and costs within this class of drugs should include generic fluoxetine in product comparisons.

■ Conclusion

Based on our analyses, citalopram has had a positive economic impact within the Texas Medicaid Program in 1999 and 2000 due to (1) its similar treatment pattern measurements and (2) its significantly lower mean costs per day associated with its use in patients. The shorter length of treatment and higher switch rate with rapid-release venlafaxine suggest poorer clinical and economic outcomes with this particular product.

DISCLOSURES

This study was supported by grants from Forest Laboratories, Inc., and the Texas Department of Mental Health and Mental Retardation, Inc., and was obtained by author M. Lynn Crismon. Crismon and author Michael T. Johnsrud have received honoraria to present the results of this research at scientific meetings. Crismon served as principal author of the study. Drafting of the manuscript was primarily the work of Johnsrud. Study concept and design, analysis and interpretation of data, and critical revision of the manuscript was the work of Crismon and Johnsrud. Statistical expertise was contributed by Johnsrud. The Texas Department of Human Services provided the database for analysis.

REFERENCES


