

Depression in Managed Care: Costs of Selective Serotonin Reuptake Inhibitors

by Bentson H. McFarland

OBJECTIVE: To review data on the comparative costs of antidepressants.

DESIGN: Review of data from articles identified in a Medline search, meeting presentations, and independent market research that are relevant to the costs associated with treating depression. Studies were included if they compared depression treatment costs with tricyclic antidepressants to those with one of the leading selective serotonin reuptake inhibitors (SSRIs) or if they compared treatment costs among the leading SSRIs. Data were extracted on drug acquisition costs, concomitant medications, dose titration, multi-tablet/multi-capsule therapy, duration of therapy, and overall treatment costs.

RESULTS: SSRIs may be more cost-effective than tricyclic antidepressants because they are associated with lower

health care utilization. Assessment of economic outcomes with SSRI therapy can be based on identified cost drivers, including dose titration and the need for multi-tablet therapy. Among the SSRIs, the use of nonpharmaceutical health care services are generally equivalent, and differences in direct drug costs may affect overall treatment costs.

CONCLUSIONS: Cost for depression treatment may be reduced by using an SSRI that is associated with a favorable profile in areas identified to influence overall treatment cost, such as dose titration, need for multi-tablet and/or multi-capsule therapy, and concomitant medications.

KEYWORDS: Depression, managed care, SSRIs

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Depression is a common and debilitating condition, affecting up to 21.3% of women and 12.7% of men in the United States at some point in their lifetimes.¹ At any given time, 10–14 million Americans suffer from major depression, and of those who initially experience a major depressive episode, more than half will eventually develop another.^{2,3}

The direct costs of treatment for major depression (including hospitalization, drug treatment, and outpatient services) combined with the indirect costs (such as decreased workplace productivity, excess absenteeism, and suicide) are significant. Greenberg and colleagues estimated the total costs of depression in the United States in 1990 at \$43.7 billion; more than half of that amount was related to indirect costs.⁴ Direct costs for the disorder are high because persons with depression use significantly more health care services than persons without depression. One study showed that the mean annual treatment cost per primary care patient with depression (\$4,246) was significantly higher than that per patient without depression (\$2,371).⁵

Patients with depression also experience an impaired quality of life. Wells and colleagues determined that these patients reported worse physical and social functioning, more pain, and worse current health; they spent more days in bed than patients with chronic medical conditions, such as hypertension, diabetes, angina, back problems, or gastrointestinal problems.^{6,7} In addition, depression can lead to absenteeism in the workplace and reduced productivity.⁸ Patients diagnosed with major depression are almost five times more likely to suffer at least one disability day (defined as being bedridden for at least part of the day or being unable to perform usual activities due to the illness) than are people without depression, and more than three times as likely to miss work because of their condition.⁸

The objective of this paper is to review data relevant to discussions of comparative costs associated with antidepressant treatment, based on published articles (as identified in a Medline search), meeting presentations, and independent market research. The paper is motivated in part by the author's observation that managed care organizations have not infrequently recommended paroxetine as a preferred agent.

Antidepressant Pharmacotherapy

The conclusions of the 1991 National Institutes of Health Consensus Panel on Diagnosis and Treatment of Depression in Late Life were re-examined by Lebowitz and colleagues in

1997.⁹ The investigators determined that, because of the complexity and impact of depression, aggressive approaches to recognition, diagnosis, and treatment are warranted to minimize suffering, improve overall functioning and quality of life, and limit inappropriate use of health care resources. Appropriate treatment of depression in the primary care setting has been associated with lower overall health care utilization.¹⁰

Pharmacotherapy, either alone or in conjunction with psychotherapy, plays an important role in the treatment and recovery of patients with depression.¹¹ Once depression has been diagnosed, the clinician should select the initial therapy based on the symptoms, the level of dysfunction, and prior episodes of depression.¹² The patient's age, comorbid conditions, and specific presenting symptoms should be taken into account by the physician when diagnosing and managing major depression.¹³ Rational selection of antidepressant medication also should include consideration of potential adverse effects and drug-drug or drug-food interactions. Acute-phase pharmacotherapy is recommended for six to eight weeks, with a continuation phase for six to nine months after remission.^{11,14}

■ ■ Tricyclic Antidepressants versus Selective Serotonin Reuptake Inhibitors

Approximately two-thirds of patients with major depression will respond to antidepressant therapy.¹⁵ The most commonly prescribed antidepressants are the tricyclic antidepressants (TCAs) and the newer-generation selective serotonin reuptake inhibitors (SSRIs), which include fluoxetine, paroxetine, and sertraline. Recently, citalopram became the fourth SSRI approved in the United States for the treatment of depression. Drugs in these two classes are widely regarded as effective in the treatment of depression; however, the SSRIs are associated with improved tolerability.^{12,15}

Although TCAs are less expensive than the SSRIs, they have deleterious side effects, including anticholinergic and cardiovascular side effects, and poorer long-term tolerability, which may ultimately result in higher overall treatment costs. The most common adverse effects of SSRIs include sexual dysfunction, nervousness, insomnia, drowsiness, fatigue, sweating, headache, and tremor. With the exception of sexual dysfunction, these effects generally are not severe enough to make the patient noncompliant and often subside as treatment continues. A major concern of therapy with the SSRIs is the potential for drug-drug interactions because of their effect on the cytochrome P450 system. This possibility is especially important in patients with cardiac disease, who often are taking multiple medications.¹⁶ Caution is urged when SSRIs are coadministered with drugs such as phenothiazines, Type 1C antiarrhythmics, and other antidepressants.

Economic Issues

Because the acquisition costs of SSRIs are higher than those of

TCAs, economic-outcome studies have been conducted to determine whether the clinical advantages of the SSRIs justify this additional cost. Prospective data, retrospective claims analysis, and cost models show that the greater acquisition cost of the SSRIs is offset by reduced medical utilization (particularly hospitalization and office visits) and decreased subsequent expenses attributable to lower incidences of adverse effects, tolerability problems, drug switching, and treatment failure with the SSRIs compared with the TCAs.¹⁷⁻²⁴ The prospective study by Simon and colleagues randomized 536 patients with depression to SSRIs or one of two TCAs and determined that antidepressant therapy with an SSRI is more likely to result in a longer duration of therapy on the original drug and a greater likelihood of receiving adequate doses compared with TCA therapy.¹⁸ In a retrospective analysis of 701 patients taking an SSRI or TCA, Sclar and colleagues demonstrated a total annual cost savings of \$313 with SSRI therapy versus TCA therapy for the treatment of patients with a diagnosis of depression (n=555).²² When patients with SSRI or TCA use for any indication were considered (n=701), the savings associated with SSRI therapy were even greater, \$367.

Henry and Rivas addressed the concern that increased emphasis on the cost of depression treatment may lead to treatment policies in which cost containment is achieved at the expense of adequate care.²⁵ The cost drivers for these changes in health care include greater accountability of health maintenance organizations (HMOs) and tighter budgets. To meet these fiscal concerns, some patients may be refused treatment or may have to avoid certain therapies to stay within set budgets. More often patients may be asked to pay for treatment. The investigators noted that although market price is only one of the many factors that should affect the prescriber, the increasing trend toward cost-containment policies is liable to lead to false economies.

■ ■ Patient Adherence

Patient adherence is a critical factor in determining the success, and ultimately the cost, of antidepressant therapy. Premature discontinuation of drug therapy is a major cause of relapse in patients who suffer from major depressive disorder.^{26,27} Discontinuation rates because of adverse effects are higher with TCAs than with SSRIs.²⁸⁻³¹ The side effects of the TCAs may cause patients to abandon treatment before reaching an adequate dosage and treatment duration. In addition, studies have suggested that antidepressant medications, particularly the TCAs, often are inadequately prescribed with respect to dose and duration, especially by nonpsychiatric physicians.^{32,33} This inadequacy may lead to a greater likelihood that patients on TCAs will discontinue antidepressant therapy early.^{34,35} Another element of therapy that may affect compliance is the dosing schedule. The simplified administration schedules of the SSRIs compared with older classes of antidepressants may help

SSRI Prescriptions Filled with More than One Tablet or Capsule per Dose and Associated Cost

	Paroxetine	Fluoxetine	Sertraline
Average daily dosage	23 mg	30 mg	101 mg
Percentage of prescriptions filled with more than one tablet	16%	50%	45%
Average daily cost/patient	\$2.01	\$3.08	\$2.38
Average 30-day cost/patient	\$60.30	\$92.40	\$71.40

Source: Viale G. An economic analysis of physician prescribing habits of selective serotonin reuptake inhibitors. *Hosp Pharm* 1998; 33: 847-50.

Note: SSRI is selective serotonin reuptake inhibitor.

improve patient compliance and reduce physician and pharmacist time, thereby potentially reducing overall cost of therapy.³⁶

■ ■ Cost Analysis of SSRI Therapy

As health care providers become more aware of the total costs for treating depression and less concerned about the simpler issue of drug-acquisition costs, the SSRIs are used more often as first-line therapy for depression and other psychiatric illnesses. The question of which particular SSRI would improve the economic outcome of treatment is challenging because of the lack of prospective comparative trials. Available data demonstrate that direct drug and overall costs associated with SSRI therapy may differ depending on which SSRI is prescribed. The cost drivers for SSRI therapy include dose titration and stratification, costs for concomitant drugs, duration of therapy, and drug acquisition costs.

Dose Titration

For several antidepressant medications, the starting dose is almost always less than the target (or therapeutic) dose. When prescribing TCAs, for example, it is common practice to begin with modest doses (such as 25 to 50 mg per day) in order to minimize adverse events like anticholinergic side effects or orthostatic hypotension. Over subsequent weeks, the dose is increased to the therapeutic range (which usually exceeds 100 mg per day). Newer generation antidepressants such as venlafaxine and nefazodone also require gradually increased dosing strategies. The process of dosage increase is referred to as dose titration. Recent work using Medicaid claims to examine antidepressant utilization by nursing home residents suggests that automated pharmacy data are reasonably accurate measures of dosing patterns.

Titration can affect the cost effectiveness of SSRIs because of the expense associated with dosage adjustments.³⁷ Higher dosages are associated with greater drug costs (particularly if multiple tablets are required to achieve the efficacious dose) and with increased provider time. Titration to achieve adequate dosage delays effectiveness and may result in premature discontinuation

because the patient gets discouraged or in excessive utilization of medical services while the patient is awaiting a response.³⁸

In a retrospective study of SSRI-associated utilization and costs in 744 patients enrolled in a network-model HMO, Sclar and colleagues showed dose titration to be the primary predictor of health care utilization associated with SSRI therapy for depression.³⁷ Dose titration rates were 16% for fluoxetine, 28% for paroxetine, and 40% for sertraline. The authors reported significantly lower overall treatment costs for fluoxetine compared with the others. This study, however, contained biases in patient selection and design that may have led to the higher titration rate for paroxetine compared with that of fluoxetine.³⁹⁻⁴¹ In the Sclar et al. study, differences were evident in average patient age, ratio of male to female patients, and degree of primary versus specialty care providers between the groups.⁴¹ This study did not control for baseline severity or consider that fluoxetine was more likely to be used as first-line therapy.^{40, 41} Higher hospital costs in the paroxetine and sertraline groups accounted for the increased overall costs compared with the fluoxetine group, which indicates that differences in disease severity and comorbid physical conditions may have been responsible for any cost variations between the groups.³⁹

More current observations indicate that the dose-titration rate for paroxetine is comparable to or even lower than that for fluoxetine and lower than that for sertraline. Russell et al. studied depression-related claims from more than 2,300 patients and reported a significantly lower rate of titration with paroxetine (36% of patients; $p=0.001$) than with fluoxetine (44%) and sertraline (48%).⁴² The titration rates for fluoxetine and sertraline were statistically similar.

A large-scale study funded by the Food and Drug Administration (FDA) at a large northwestern HMO reported that 64% of patients taking fluoxetine required doses higher than the recommended starting dose, compared with only 47% of patients taking paroxetine.⁴³ This study analyzed antidepressant utilization for any indication. Another analysis of SSRI prescriptions in a primary care medical group revealed similar titration rates for fluoxetine ($n=177$) and paroxetine ($n=175$),

Relationship between Dose Titration and Direct Drug Costs for SSRI Therapy in a Managed Care Setting

	Paroxetine	Fluoxetine	Sertraline
Average daily dosage	21 mg	25 mg	81 mg
AWP for recommended daily starting dose ^a	\$1.85/20 mg	\$2.16/20 mg	\$1.94/50 mg
Actual daily AWP	\$1.95	\$2.61	\$3.16
Actual AWP for 30-day supply	\$58.50	\$80.70	\$94.80

Source: Smith W and Sherrill A. A pharmacoeconomic study of the management of major depression: patients in a TennCare HMO. *Med Interface* 1996; 9: 88-92.

Notes: AWP is average wholesale price. SSRI is selective serotonin reuptake inhibitor.

^aBased on AWP from 1994.

20% and 22%, respectively, and a higher rate for sertraline (n=98; 28%).⁴⁴ The titration rate was 40% for TCAs (n=373) and 33% for other antidepressants (n=119). Patients in this study were members of one of two managed care plans that had open formularies with no restrictions on SSRI selection. Preliminary data from a long-term care setting showed a lower rate of dose titration with paroxetine (18%) compared with other SSRIs (24% for sertraline and 29% for fluoxetine).⁴⁵ The rate of dose titration with sertraline is consistently the highest in the class, suggesting that this drug is associated with the highest costs for titration.

■ Multi-Tablet Doses

Russell and colleagues examined SSRI treatment courses and costs and found that the higher total cost of treatment with fluoxetine (\$1,385 ± \$2,221) compared with paroxetine (\$1,231 ± \$1,690) and sertraline (\$1,203 ± \$1,555) was related to significantly higher pharmaceutical costs, not expenses for other depression-related health care.⁴² Mean pharmaceutical costs were \$586 ± \$430 in the fluoxetine group, \$446 ± \$342 in the sertraline group, and \$419 ± \$320 in the paroxetine group (p<0.001 for fluoxetine). In this study, costs for hospitalization, outpatient care, and laboratory services were similar for all three SSRIs.

Pharmaceutical costs were significantly higher in the fluoxetine group compared with the paroxetine and sertraline groups because a significantly higher percentage of patients taking fluoxetine required multicapsule therapy (about 35%) compared with patients taking paroxetine or sertraline (about 18% and 22%, respectively). Data from an outpatient psychiatric pharmacy also demonstrated that daily dosage and the combination of pills necessary to achieve the effective dose were important factors in determining SSRI costs.⁴⁶ The author analyzed physicians' prescribing habits for SSRIs for any diagnosis (n=4,074) and found that only 16% of patients on paroxetine took multi-

ple tablets, whereas about half of the patients on fluoxetine and sertraline received multiple tablets (see Table 1, page 144). The mean daily dosage of paroxetine was 13% higher than the recommended starting dose compared with 53% higher for fluoxetine and 100% higher for sertraline.

In the FDA-funded study, almost 90% of the patients taking paroxetine received dosages that were maintained with a single tablet (40 mg/day), compared with only 37% of patients taking fluoxetine (20 mg/day).⁴³ Similar results were reported by Baum.⁴⁷ In this study, almost every patient receiving paroxetine was prescribed a daily dosage that required taking only one tablet compared with about 85% of patients taking sertraline and 60% of those taking fluoxetine.

Recently, the manufacturer of fluoxetine introduced a 40-mg capsule of this SSRI, but this higher capsule strength is priced similarly to two 20-mg capsules.

Concomitant Drugs

The cost of concomitant psychotropic drugs used in the treatment of depression (such as anxiolytics and/or sedatives/hypnotics) must also be considered in the cost analysis of SSRI therapy. Navarro and colleagues examined SSRI utilization for any indication in two managed care models and reported a variation in costs between the two plans for concomitant medication to treat adverse effects.⁴⁸ In a staff-model HMO, paroxetine was associated with slightly higher costs for concomitant anxiolytic therapy compared with fluoxetine and sertraline. According to the authors, this outcome was unexpected because paroxetine is associated with the lowest incidence of anxiogenic side effects among the available SSRIs. The authors suggest that this result may be attributable to the fact that patients with anxiety receive concomitant anxiolytic therapy and are prescribed paroxetine because it does not worsen anxiety symptoms. In the independent provider association, paroxetine was associated with

the least expensive cost for anxiolytics and sedatives/hypnotics, whereas sertraline was associated with the highest cost for these concomitant medications. A study on the utilization of SSRIs in a managed care plan in Hawaii showed that total costs for concomitant medications were comparable for all SSRIs.⁴⁹

Duration of Therapy

Conflicting evidence has been published regarding the effect of duration of SSRI therapy on health care costs. Thompson et al. examined SSRI treatment courses for depression and divided utilization into five categories: early discontinuation (n=229), switching/augmentation (n=244), upward titration (n=311), partial compliance (n=251), and three-month use (n=122).⁵⁰ Longer duration of therapy was associated with the lowest overall treatment costs. Most of the prescriptions studied were for fluoxetine (88%); paroxetine was not available at the time of the analysis. In the study conducted by Russell and colleagues, the relationship between length of therapy and overall treatment costs was not evident.⁴² The critical consideration is that the duration of therapy for all SSRIs is often shorter than the target for antidepressant maintenance therapy recommended in national treatment guidelines for depression.^{43, 44, 48} For instance, in their examination of antidepressant use and costs in an HMO, Johnson et al. found that although the dose of SSRIs used to treat patients was generally adequate, the mean duration of use was shorter than recommended.⁴³ Inadequate treatment duration may result in high relapse rates for depression.

Drug Acquisition Costs

Among the SSRIs approved for depression, citalopram and paroxetine have the lowest acquisition costs based on average wholesale prices (AWPs), about 23% and 12% less, respectively, than fluoxetine.⁵¹ Analysis of antidepressant prescribing in a Medicaid managed care setting demonstrated how AWP and dose titration contribute to the actual monthly cost. Smith and Sherrill calculated the mean daily cost using AWP and average daily dosage and reported that the average cost of paroxetine was 37% lower than that of fluoxetine and 65% lower than that of sertraline, because the maintenance dose of paroxetine was closest to the recommended starting dose (see Table 2, page 145).¹⁹

Discussion of acquisition costs associated with SSRI therapy must acknowledge that the newest entry in this class, citalopram, is priced lower than drugs that have preceded it to market; this has been the trend in pricing the SSRI class to facilitate market penetration. Although citalopram is competitively priced, dose titration may influence treatment costs for patients receiving this product. The recommended daily starting dosage of citalopram is 20 mg, but the 40-mg tablet strength has been shown to be significantly more effective in treating depression.⁵²⁻⁵⁴ Of the five citalopram studies included in materials submitted by the manufacturer to the FDA, four showed no dif-

ference in efficacy of 20 mg compared with placebo, and three showed no difference in the efficacy of 40 mg compared with placebo. Another report recommended 40 mg/day as the usual dosage for citalopram.⁵⁵ Thus, comparative research with all SSRIs is recommended to determine the dose titration rate for patients on citalopram and its effect on treatment costs.

Other Important Issues

Pill Splitting

Some organizations have introduced tablet-splitting policies to control pharmaceutical costs within the SSRI class. Such policies are unappealing to patients and may result in improper dosing. One study investigated the accuracy of tablet splitting among 94 healthy patients who were each asked to split 10 25-mg tablets of hydrochlorothiazide.⁵⁶ Almost all patients (97%) expressed a preference for commercially available lower dose formulations over the use of split tablets, and 77% said they would be willing to pay more for lower dose formulations. In addition, 41% of the 1,752 manually split tablet portions deviated from the ideal tablet weight by more than 10%, and more than 23% deviated by more than 15%.⁵⁶ The acceptable level of deviation specified by the United States Pharmacopeia is $\pm 10\%$. Even when a tablet splitter was used, accuracy of tablet splitting was poor (more than 37% deviated by more than 10%). Elderly patients have particular difficulty splitting tablets.⁵⁷

A recent study investigated tablet splitting among 12 psychotropic medications, including paroxetine and sertraline, and identified the potential for cost savings. Results indicated that if all eligible prescriptions were used in split dosages, consumers could save about \$1.45 billion annually. If the pill splitting were limited to paroxetine and sertraline, the savings would equal approximately \$920 million.⁵⁸ Another study conducted by Fawell et al. investigated tablet splitting in patients prescribed fosinopril sodium, an angiotensin-converting-enzyme inhibitor. Of 105 patients in the study, 47 split their tablets and 58 did not. Results for the two groups were similar in median compliance: 90.5% for tablet-splitters and 91.7% for those patients not splitting tablets. Results also indicated a 50% reduction in annual acquisition costs for those patients splitting fosinopril tablets.⁵⁹

It is arguable whether patient issues with tablet splitting may negatively influence compliance and dosage levels because patients may opt to take whole tablets every other day instead of half tablets daily as prescribed.⁵⁶ These data suggest tablet-splitting policies may require further research in clinical and economic outcomes, because the degree of compliance with antidepressant therapy is directly proportional to efficacy and treatment cost.²⁸⁻³⁰

Managed Care Issues

Differences among the SSRIs in key cost drivers may influence

formulary decisions and positioning. According to one audit of formulary position for SSRIs, paroxetine was listed as a preferred SSRI on 85% of HMO and pharmacy benefit management (PBM) formularies, fluoxetine appeared as a preferred SSRI in 23% of formularies, citalopram on 62%, and sertraline on 64%.⁵⁸

Another important consideration in the managed care setting is patient satisfaction, which has taken on a greater relevance as patients have assumed more responsibility for their own care. A recent survey of 1,454 managed care patients with depression found that 61% of patients taking paroxetine were highly satisfied with their antidepressant medication, a significant difference compared with 48% of those taking fluoxetine and 43% of those taking sertraline.⁵⁹ The study, which found that patients generally perceive their depression treatment to be inadequate, also reported that a smaller percentage of patients taking paroxetine (26%) experienced decreased school or work productivity because of depression, compared with patients taking sertraline (40%) or fluoxetine (49%).

■ ■ Conclusion

The data are both limited and subject to publication bias.⁶⁰ One can, nonetheless, draw a few conclusions and form some impressions about medications for treatment of depression in a managed care environment.

When overall health care utilization and expenses are considered, SSRI therapy is associated with comparable or lower costs compared with the lower-priced TCAs. The SSRIs are now used widely as first-line therapy because they are as effective clinically as the TCAs, have fewer side effects, are easier to administer, and are safer in overdose situations. Data that reflect current prescribing and clinical and economic outcomes of SSRI therapy are derived from retrospective claims analysis and demonstrate that costs associated with SSRI therapy may be based on dose titration, the need for multiple tablets, cost of concomitant medications, drug acquisition cost, and duration of therapy. Fluoxetine and paroxetine are associated with the lowest incidences of dose titration. Single-tablet maintenance regimens are most likely to be achieved with paroxetine therapy. Conflicting results have been published regarding the costs of concomitant medications. Of the SSRIs, citalopram and paroxetine are associated with the lowest acquisition costs based on AWP.

Duration of therapy for SSRIs is often shorter than the recommendations for antidepressant maintenance therapy found in national treatment guidelines. Treatment duration is an area for continued research and physician education. Further investigation into the comparative treatment costs of SSRI therapy is required because current evidence suggests that nonpharmaceutical costs associated with available products are similar and that variations in drug costs may influence overall economic outcomes for the treatment of depression.

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