Cost-Effective Treatment of Depression with Selective Serotonin Reuptake Inhibitors

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Objective: To compare factors that influence cost of antidepressant therapy between older tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) and among drugs in the SSRI class.

Study Design: Literature review.

Results: Pharmacoeconomic data from the primary care and managed care settings demonstrate that the higher acquisition cost of the SSRIs is offset by reduced medical utilization because of a lower incidence of treatment-related adverse events, drug switching, and dosage adjustments than among patients taking TCAs. Analysis of pharmacy claims data suggests that drug acquisition costs, use of concomitant medications, incidence of dose titration, frequency of multitablet therapy (dose stratification), and duration of therapy are the key factors in determining the cost of SSRI therapy. Among the established SSRIs, drug acquisition costs are lowest for paroxetine and sertraline. Costs for concomitant medications may vary by healthcare plan. Recent reports indicate that paroxetine is associated with a low incidence of dose titration. Paroxetine and sertraline are available in extended dosage forms to reduce the need for multitablet therapy. Duration of therapy with all SSRIs is typically shorter than recommended.

Conclusion: Antidepressant therapy with SSRIs has been shown to be more cost effective than treatment with TCAs when overall healthcare utilization and expenses are considered.

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Patients with depression utilize significantly more healthcare services, are more expensive to manage, and experience significantly poorer quality of life compared with patients without depression.[1-7] Major depression is quite common, affecting 1 in 10 US adults per year and approximately 1 in 5 over the course of their lifetimes, according to the National Comorbidity Survey of adults age 18 to 54 years.[8] Women are more likely than men to experience a lifetime major depressive episode, with a prevalence of 21.3% versus 12.7%, respectively. In the primary care setting, about 20% of patients may have current depression[9] or clinically significant depressive symptoms.[10]

Utilization of healthcare services by patients with depression is significantly greater than that by patients without depression, leading to higher healthcare costs for patients with the disease. Simon and colleagues reported that the mean annual cost per patient with depression ($4246) was significantly higher than that for patients without depression ($2371).[11] The increased cost for patients with depression was significant across all categories of care ($P < .001$), was evident over the 12 months of the study, and was related to greater use of medical services rather than psychiatric services (**Figure 1**). After adjustment for chronic medical comorbidity, the treatment costs for patients with depression were typically 50% higher than those for patients without depression. Another study found that one fourth of high utilizers of medical care services had a current diagnosis of depression, and two thirds of the high utilizers reported at least 1 depressive episode in their lifetime.[12] In this study, distressed high utilizers reported significantly poorer overall health ($P < .001$) and were more likely to report the prevalence of chronic medical conditions compared with nondistressed high utilizers ($P > .05$). Kroenke and colleagues examined the 15 most common physical

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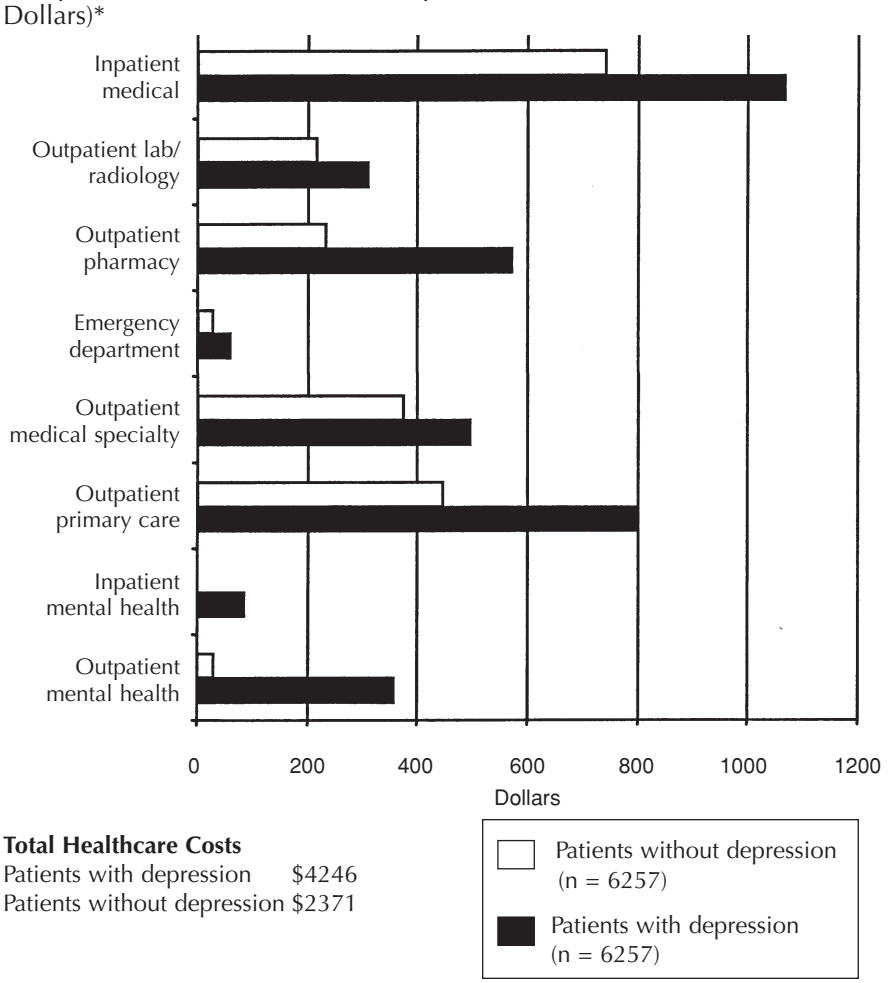
symptoms for which patients visit their primary care physician and found that the symptoms were somatoform in 16% to 33% of cases.[13] In this study, the number of physical symptoms was directly proportional to the risk of psychiatric illness and functional impairment.

Because of the prevalence of depression and the high rate of possibly inappropriate utilization by patients with the disease, the economic impact of depression is substantial.[14] Greenberg and colleagues estimated the total costs of depression in the United States at $43.7 billion for 1990.[15] Fifty-five percent of these costs are indirect costs related to lost productivity and absenteeism. Direct expenditures (medical, psychiatric, and drug expenditures) account for 28% of the total, and 17% is related to mortality costs. Mortality is an important consideration in the analysis of the overall impact of depression because about 15% of patients with major depression commit suicide.[16] Depression may be as costly as common physical diseases. First Chicago Corp., a bank holding company, reported direct costs of about $927,000 in mental health claims and an estimated $1.2 million in heart disease claims over a 1-year period.[17] In this study, depression was associated with more disability days per episode and higher 12-month relapse rates than chronic medical diseases such as diabetes, heart disease, and lower back pain.

Additionally, the impact of depression on patient functioning and well-being is greater than that for many chronic medical conditions, including hypertension, diabetes, arthritis, back problems, lung problems, and gastrointestinal problems, according to the Medical Outcomes Study.[18] Compared with patients with depression, only those with current heart conditions (ie, angina and coronary artery disease) experienced poorer overall functioning and well-being. This large-scale, 11,242-patient study based its findings on self-administered patient questionnaires covering physical, social, and role functioning; bodily pain; number of bad health days; and current health.

In the workplace, depression can greatly impair productivity and increase absenteeism.[19] Compared with asymptomatic patients, patients with a diagnosis of major depression are almost 5 times more likely to experience at least 1 disability day and more than 3 times as likely to miss work because of their condition. The numbers of disability days and missed workdays were also higher in those with minor depressive symp-

Figure 1. Increased Utilization and Costs in Patients With Depression Compared With Patients Without Depression Over 12 Months (Mean Dollars)*



Total Healthcare Costs

Patients with depression	$4246
Patients without depression	$2371

*$P < .001$ for all cost categories.
Source: Adapted from reference 11.

toms compared with asymptomatic patients. In this study, a disability day was defined as being bedridden for at least part of the day or being unable to perform usual activities because of illness.

··· BENEFITS OF TREATMENT ···

Antidepressant pharmacotherapy in the primary care setting has been shown to effectively reduce healthcare utilization and cost. A 6-month, open-label study examined 20 patients with a confirmed diagnosis of depression and found that antidepressant pharmacotherapy with either a selective serotonin reuptake inhibitor (SSRI) or a tricyclic antidepressant (TCA) reduced healthcare utilization.[20] For patients in this study, the mean daily cost for use of healthcare services at the health maintenance organization (HMO) was $12.55 ± $6.36 during the 6-month study, a decrease of about 5.5% compared with the 6 months before the study. When treatment costs for the study were not included, the mean cost declined almost 50% to $6.75 ± $6.26 per day. Antidepressant treatment significantly improved scores on the Hamilton Depression Scale (scores went from 17.61 ± 4.35 to 9.82 ± 5.87; $P < .001$) and on the Medical Outcomes Study survey for social functioning, general health, mental health, physical functioning, emotional role functioning, and vitality ($P < .05$ for each variable). Improvements also were seen in the rate of absenteeism (0.25 days per month compared with 1.31 days per month at baseline) and level of impairment at work (10% of patients compared with 40% at baseline; $P < .03$).

The beneficial effect of treatment of depression on work productivity was observed in a study of 493 patients with depression who were treated with antidepressant therapy over 12 weeks. In this study, a 1-point improvement in scores on the Hamilton Depression Scale resulted in a 2% increase in work performance.[21,22] On average, work performance improved 25.7% after treatment, with more than half of the improvement occurring within the first 4 weeks after initiation of treatment. After 12 weeks, 84.4% of treated patients reported improved work performance, and almost 90% demonstrated reductions in depression symptom scores. Advances in work productivity associated with antidepressant treatment seem to be related to the degree of symptom improvement.[23,24]

Although larger studies are needed, these data indicate the breadth of benefits associated with the identification and treatment of patients with mental disorders, particularly in relation to workforce-related issues of productivity and absenteeism, which account for the largest portion of depression-related costs.[15,25] They also point to a high level of unnecessary impairment because 50% to 60% of depression cases may be undiagnosed or misdiagnosed.[9,26] About half of all primary care physicians may intentionally misdiagnose depression for patients who meet diagnostic criteria for the disease because of uncertainty about the diagnosis or problems with reimbursement for services related to a depression diagnosis.[26] Such practices led to improper diagnosis codes for 31% of patients. Data that show a high rate of somatization associated with physical symptoms also indicate that depression is frequently misdiagnosed.[13] This apparent unfamiliarity and discomfort with psychiatric diagnoses in the primary care setting, particularly depression, may explain why up to 60% of patients with a psychiatric illness have never received any professional psychiatric care.[8] In effect, overall awareness of depression remains alarmingly low, and patients frequently receive inadequate care because of patient-, provider-, and healthcare-system–related obstacles.[1] One costly result of the inadequate treatment of depression is the increased risk of suicide,[27-29] which represents a key component of depression-related costs.[15] The rate of suicide among patients with depression or anxiety disorders is high, but studies show effective use of pharmacotherapy may reduce the suicide rate among this population of patients.[27,28,30]

··· COST OF TREATMENT: NEW VERSUS OLD PHARMACOTHERAPIES ···

The introduction of the SSRIs coincided with a marked shift in the recognition and treatment of depression and anxiety. A large-scale, 8-year study at a 390,000-patient HMO in the Northwest reported that antidepressant utilization tripled since the SSRIs were introduced, most likely because of physicians' increasing familiarity with the need to accurately diagnose and treat depression.[31] As expected, the SSRIs, representing a new therapeutic class, exhibited the fastest growth rate in prescriptions, although prescription volume for all classes of antidepressants increased. This increase has prompted significant debate over cost effectiveness of the new drugs compared with the older generations of antidepressants.

Comparisons of the cost effectiveness of the SSRIs versus that of the TCAs assumes that these 2 drug classes are clinically efficacious in the treatment of depression.[32] Available comparisons also lack rigorous control over the prescribing of 1 antidepressant instead of another because of patient factors (eg, disease severity and comorbid conditions), physician variables (eg, specialty or comfort level with antidepressant classes), or medication issues.[33] In general, the reported difference in treatment costs between the SSRIs and TCAs is related to the improved tolerability of and less need for titration with the SSRIs. This results in better disease management and significantly fewer treatment-related adverse effects, including fewer anticholinergic effects with SSRI therapy compared with TCA therapy.[34] Some studies show the improved tolerability and less frequent titration of SSRIs also may reduce the rate of early discontinuations,[34-37] although a recent meta-analysis reported no significant difference in discontinuation rates between the 2 drug classes despite differences in types of adverse effects.[38]

Analysis of economic outcomes in the treatment of depression must be based on total healthcare expenditures, not medical and pharmaceutical costs separately.[39-41] Recent economic outcome studies indicate that the higher acquisition cost of the SSRIs is offset by reduced medical utilization, particularly hospitalization and office visits, because of lower incidences of adverse effects, tolerability problems, drug switching, and dose titration with the SSRIs compared with the TCAs.[34,35,42-48] Subsequently, antidepressant therapy with an SSRI is more likely to result in longer duration of therapy on the original drug, greater likelihood of receiving adequate doses, and improved disease management of depression.[35] In addition, the risk of absenteeism from work among patients taking TCAs was 2.45 times higher than that among patients taking an SSRI.[49] Further research is needed to determine whether there are differences in patient compliance between the 2 groups, as reported in another study.[50] Key findings of some of these studies are presented in the following section.

Cost Advantage of SSRI Therapy

Sclar et al studied healthcare utilization in 701 patients who received antidepressant therapy from a large HMO (400,000 members).[41] For a diagnosis of depression, the direct costs after 1 year for patients receiving an SSRI (fluoxetine) were $313 less than those for patients in the TCA group ($P \leq .05$). Higher hospitalization rates in the TCA group accounted for most of the difference (**Figure 2**). When costs were analyzed for patients receiving antidepressant therapy for any indication (including depression), the overall cost savings associated with SSRI versus TCA therapy were even greater, totaling $367 after 1 year ($P \leq 0.05$). This study also observed that optimal compliance with antidepressant therapy was associated with a lower level of healthcare utilization.

Skaer and colleagues reported similar significant cost offset with the SSRI sertraline compared with TCAs.[46] In this multivariate regression analysis, total 1-year treatment costs with SSRI therapy were $168 less than those with TCA therapy ($P \leq .05$), owing largely to reduced utilization of and costs for physician visits and hospitalizations. Additionally, patients who received the SSRI were more likely to receive at least 3 consecutive prescriptions for an antidepressant ($P \leq .05$), which suggests improved adequacy of treatment.

A study designed to mimic real-world treatment practices for depression found no significant difference in overall treatment costs with SSRI versus TCA therapy, indicating that higher pharmaceutical costs for the SSRIs were offset by lower healthcare utilization.[35] Clinical efficacy and quality of life also were similar between both treatment groups, but patients in the SSRI group had fewer adverse effects, a longer duration of antidepressant therapy, and a greater likelihood of reaching adequate doses compared with those in the TCA group.

Other observations suggest that continuation of treatment may be a significant contributor to overall direct healthcare costs for the treatment of depression with TCAs.[47,51] In these studies, the annual direct costs with SSRI therapy were about 5%[51] to 20%[47] lower than those with TCA therapy. The Canadian cost-analysis model concluded that the likelihood of continuing on a therapy was inversely related to the overall cost of care, while drug price and relapse rates were not predictive of cost.[51] The higher treatment success rate with SSRI therapy reduced the need for costly therapy switching, physician visits, and hospitalizations. Continuation of therapy for depression may affect outcome because of the high relapse and recurrence rate; 30% of patients with depression relapse within 1 year, and 75% will experience recurrent depressive episodes 10 years after the index episode.[52]

Another important factor that may contribute to the economic impact of antidepressant therapy is the ability to attain appropriate dose levels when starting therapy, as defined by minimum adequate dose according to the American Psychiatric Association's depression treatment guidelines and minimum adequate duration (90 days of continuous therapy).[53] In a study at a 143,000-patient, group-model HMO, 2139 initial prescriptions for antidepressants were studied, 865 (40%) of which accompanied a diagnosis of depression. Fifty-nine percent of patients receiving an SSRI received appropriate therapy, compared with only 47% of patients on secondary amine TCAs, 44% on tertiary amine TCAs, 37% on bupropion, and 35% on trazodone. A second study also reported significantly higher ratings for adequate dosage, duration, and trial period with the SSRIs compared with other antidepressants.[54] These data may be valuable in pharmacoeconomic discussions because therapy of at least 6 months' duration is associated with a cost offset,[55] whereas patients with depression who receive inadequate therapy or no therapy utilize significantly more healthcare services,[56,57] have more frequent somatic complaints, and remain at increased risk for suicide and continued occupational and functional impairment.[57] It is difficult to determine whether the reported treatment inadequacy with TCAs is related to specific drug characteristics of TCAs or insufficient physician and patient education.

··· COST ANALYSIS AMONG THE SSRIs ···

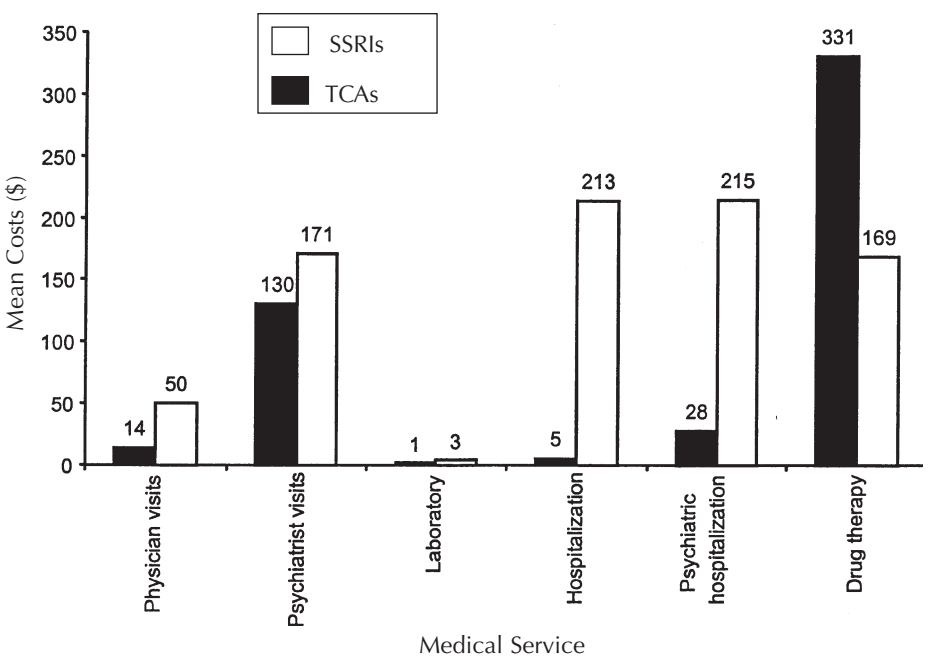
The SSRIs—fluoxetine, paroxetine, and sertraline are the leading products in the class—are increasingly used as first-line therapy for the treatment of depression and other psychiatric illnesses. The efficacy and safety of the SSRIs are similar across the class, for which the most common side effects include nervousness, nausea, insomnia, drowsiness, fatigue, sweating, headache, and tremor.

The direct (**Table 1**) and overall costs of SSRI therapy, however, may differ depending on which SSRI is prescribed. These differences in SSRI costs are related to drug acquisition cost (average wholesale price [AWP]), the cost for concomitant medications, the incidence of dose titration, and dose stratification (the percent breakdown of patients maintained at different dosages), and duration of therapy.

Drug Acquisition Cost

Direct comparison of AWPs shows that paroxetine and sertraline cost about 14% and 12% less, respectively, than fluoxetine (Table 1).[58] Citalopram, the fourth SSRI approved for treatment of depression, is priced lower than SSRIs that preceded it to market. Product labeling for citalopram and an independent report[59] on the drug suggest that the higher 40-mg dose is more effective than the recommended starting dosage of 20 mg, which indicates a need for further research on the effect of dose titration and

Figure 2. Reduced Utilization of Services with SSRI Therapy Compared With TCA Therapy in the Treatment of Depression (Regression Analysis)



Total Savings with SSRI Therapy vs TCA Therapy = $313 ($P \leq .05$)

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
Source: Adapted from reference 41.

other factors on treatment costs with this SSRI. Caution must be used in comparing drug acquisition costs alone, however, because published AWPs do not reflect discounts and rebates negotiated with the manufacturers or the need for single or multiple tablets to achieve the therapeutic dose.

Drug acquisition costs can be alleviated somewhat through contracted rebates and discounts, unitary pricing policies, and extended dosage strengths. Paroxetine and sertraline are available in extended dosage strengths that have near-unitary pricing. Some organizations also have attempted to control the cost of SSRI therapy by encouraging use of split tablets to achieve the prescribed dose[60]; however, such policies are poorly received by patients[61] and may be difficult for elderly patients to comply with.[62] In 1 study with 94 healthy volunteers who were asked to split a tablet of a cardiovascular medicine, 97% said they would prefer commercially produced lower-dose tablets, and 77% expressed willingness to pay more for lower-dose tablets instead of splitting the tablets.[61] Of approximately 1750 manually split tablets in this study, more than 41% deviated from the ideal half-tablet weight by more than 10% (the acceptable level of deviation according to the US Pharmacopeia), and about one third deviated by more than 15%. Another risk for inaccurate dosing arises because patients may decide to take a whole tablet every other day instead of a half tablet every day.

Cost of Concomitant Medications

The percentage of and financial impact from patients taking SSRIs who also receive concomitant medications may differ by the type of managed care organization. For example, Navarro et al studied SSRI utilization in 2 HMO models: an independent pracice association (IPA)-model plan and a staff-model plan.[63] In the IPA-model plan, the daily cost for concomitant medications ranged from $0.82 for paroxetine to $1.91 for sertraline. In the staff-model plan, these costs were much lower, at $0.48 for fluoxetine and sertraline and $0.55 for paroxetine (**Table 2**) (anxiolytic therapy only). The authors noted that the finding that paroxetine had the highest cost for concomitant anxiolytic therapy in the staff model was not expected because paroxetine may have a lower incidence of central nervous system stimulation compared with other SSRIs.[63] The authors suggested this finding may be because patients with anxiety already receive anxiolytic therapy as part of their treatment and then are prescribed paroxetine. They recommended further investigation into this area. The percentages of patients on concomitant medications ranged from about 4% in the IPA-model HMO to about 30% in the staff-model HMO.

According to a study by Thompson and colleagues, concomitant medications are a key factor in overall costs for SSRI therapy.[64] In this study, patients were grouped into 1 of 5 categories based on pattern of SSRI use over the 12-month follow-up period: Early discontinuation (no more than 60 days of therapy), switching/augmentation (change in antidepressant or addition of another antidepressant), upward titration, partial compliance (gap of at least 15 days in treatment), and 3-month use (90 days of continuous therapy with no switches, augmentations, gaps, or dose titration). Patients who did not meet these criteria were classified as "other." The highest mean overall treatment cost was for those in the switching/augmentation group: $7590 over the 12-month study period. However, it was not reported what portion of this cost was related to augmentation. These results should be interpreted with caution because 88% of the 1200 patients studied received fluoxetine, compared with only 12% who received sertraline. Paroxetine and other SSRIs were not included in the analysis. Thus, the findings may be more indicative of con-

Table 1. Average Wholesale Prices for Recommended Starting Doses of SSRIs

SSRI	Recommended Starting Dose	Average Wholesale Price ($)/ Tablet or Capsule*	Usual Effective Dose or Dosage Range
Citalopram	20 mg	1.97	40 mg
Fluoxetine	20 mg	2.59	20-30 mg
Paroxetine	20 mg	2.23	20-30 mg
Sertraline	50 mg	2.27	100-150 mg

SSRI = selective serotonin reuptake inhibitor.
*Price is given for the recommended starting dose.
Sources: References 58 and 59.

comitant medications or drug switching as a cost driver associated with fluoxetine therapy rather than SSRI therapy in general.

Overall, data on concomitant drug usage vary substantially. Use of a second antidepressant (a TCA or trazodone) in combination with an SSRI was reported in about 6% of patients in one study, ranging from 4.5% for sertraline to 7.4% for fluoxetine.[43] It is very likely that these agents were used for their hypnotic effects.[65] In a review of a claims database with 110,000 patients, the percentage of patients on SSRIs and concomitant anxiolytics was similar for fluoxetine, paroxetine, and sertraline at about 10%.[66] Another database review indicated that between 33% (fluoxetine) and 42% (paroxetine) of patients on SSRIs also received concomitant anxiolytic or hypnotic therapy. An even higher level of concomitant medication usage with SSRI therapy was reported in a study of patients receiving either sertraline or fluoxetine. In this study, approximately 60% of patients received concomitant hypnotic therapy[65] Other SSRIs were not studied.

Dose Titration and Dose Stratification

The expenses associated with dosage adjustments include provider costs and pharmaceutical costs. McFarland estimated the provider costs at $50 per visit for the clinician, $10 per visit for the pharmacist, and $5 per visit for the pharmacy technician.[40] Higher drug doses are associated with higher drug acquisition costs, particularly when multiple tablets are required to achieve the efficacious dose. Dose stratification is the concept explaining the percentage of patients who require multiple tablets, and it will be discussed with titration because the 2 areas are closely related.

A study by Sclar and colleagues showed dose titration of SSRIs to be the primary predictor of healthcare utilization.[67] This study reported titration rates of 16%, 28%, and 40% for fluoxetine, paroxetine, and sertraline, respectively, and concluded that the lower titration rate for fluoxetine resulted in lower overall treatment costs over a 1-year period.[67] Although the Sclar et al study contained methodological flaws in patient selection[68] and did not control for baseline disease severity or the greater likelihood that paroxetine and sertraline were used as second-line treatments because they were newer antidepressants,[48] the study demonstrated that dose titration is critical in analysis of SSRI cost effectiveness.

A more recent report from Russell et al examined the course and cost of SSRI treatment in 2342 fee-for-service patients and reported that paroxetine was associated with a significantly lower dose titration rate (36%) than fluoxetine (44%) and sertraline (48%), whereas the titration rates for fluoxetine and sertraline were similar.[69] In this study, the critical cost factor was the percentage of patients who required 2 or more tablets

Table 2. SSRI Utilization in an IPA-Model and a Staff-Model HMO After 60 Days of Antidepressant Therapy

	Type of HMO		
	IPA Model		
Utilization Variable	**Paroxetine (n = 461)**	**Fluoxetine (n = 1663)**	**Sertraline (n = 1481)**
Average daily dose (mg)	22	23	71
SSRI discontinuation rate (%)	46	37	54
Daily cost for concomitant anxiolytic therapy ($)	0.72	0.95	0.97
Daily cost for concomitant sedative/hypnotic therapy ($)	0.10	0.27	0.94
	Staff Model		
	Paroxetine (n = 65)	**Fluoxetine (n = 556)**	**Sertraline (n = 171)**
Average daily dose (mg)	20	23	61
SSRI discontinuation rate (%)	54	37	57
Patients switched to another SSRI (%)	15	4	9
Daily cost for concomitant anxiolytic therapy ($)	0.55	0.48	0.48

HMO = health maintenance organization; IPA = independent practice association; SSRI = selective serotonin reuptake inhibitor.
Source: Adapted from reference 63.

per day to achieve the therapeutic dose. This percentage was significantly higher for fluoxetine (35%) compared with paroxetine (19%) and sertraline (22%). This difference resulted not only in significantly higher pharmaceutical acquisition costs in the fluoxetine group but also in higher overall treatment costs with fluoxetine compared with the other 2 groups. Costs for outpatient, hospital, and laboratory services were similar among all 3 groups.

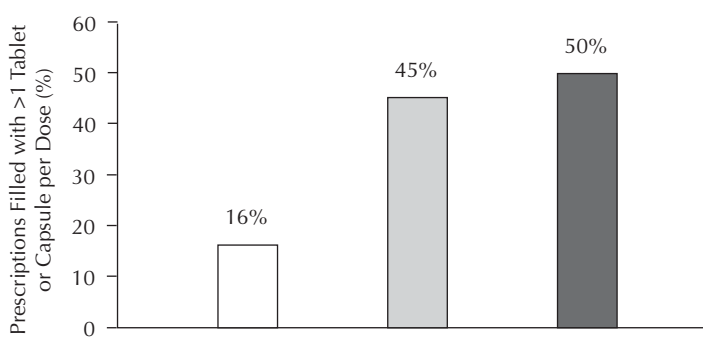
A study funded by the Food and Drug Administration of more than 18,000 patients analyzed antidepressant utilization in a large group-model HMO over 8 years and reported similar findings regarding dose titration and stratification of fluoxetine and paroxetine.[31] This study revealed substantial differences within the class for dose titration rates and the need for multiple tablets to achieve therapeutic dosages. More than 50% of patients on paroxetine were maintained at the recommended starting dose of 20 mg/day, compared with about one third of those on fluoxetine, which also has a recommended starting dose of 20 mg/day. The percentage of patients who were maintained on a dosage that required a single tablet was about 90% for paroxetine and only 36% for fluoxetine. The study reported that about three fourths of patients taking sertraline (recommended starting dose of 50 mg/day) received dosages between 50 and 150 mg/day, but this does not accurately reflect titration rates or the need for multiple tablets to achieve the therapeutic dose. However, the authors noted that sertraline was associated with the highest mean dose and treatment cost per day.

Viale investigated dose titration and need for multiple tablets in a psychiatric facility of a California medical center and reported that the daily dose and the combination of pills needed to achieve the effective dose are important factors in determining overall cost associated with SSRI therapy.[70] Analysis of physician prescribing habits revealed that only 16% of patients on paroxetine required multiple tablets to reach the target dose, compared with about 50% of patients on fluoxetine and sertraline who received either multiple or split tablets (**Figure 3**). In this study, titration was less frequent with paroxetine based on the observation that the mean daily dose of paroxetine was 13% higher than the recommended starting dose, compared with 53% and 100% higher for fluoxetine and sertraline, respectively. The average daily direct cost for paroxetine was 16% lower than that for sertraline and 38% lower than that for fluoxetine.

Analysis of antidepressant utilization in a Medicaid managed care setting yielded similar findings regarding dose titration.[43] The average daily dosage of paroxetine was only 5% higher than the recommended starting dosage, whereas it was 25% higher for fluoxetine and 63% higher for sertraline. Thus, the actual daily cost of paroxetine (compared with that of the other 2 SSRIs) was closest to the AWP of the starting dose. Navarro and colleagues reported that sertraline was associated with the highest mean daily dose, while doses for paroxetine and fluoxetine remained relatively stable (Table 2).[63]

The issue of dose titration and multitablet therapy is important in discussions of SSRI treatment costs because data indicate that more frequent use of paroxetine or sertraline (which are available in extended-dose formulations) rather than fluoxetine can produce substantial cost savings.[60,71,72]

Figure 3. Physician Prescribing Habits for SSRIs: Dose Stratification and Use of Multiple Tablets



	Paroxetine	Sertraline	Fluoxetine
Average daily dosage	22.6 mg	100.6 mg	30.5 mg
Average daily cost/patient	$2.01	$2.38	$3.08
Average 30-day cost/patient	$60.30	$71.40	$92.40

SSRI = selective serotonin reuptake inhibitor.
Source: Adapted from reference 70.

Duration of Therapy

Studies that have examined duration of SSRI therapy reported that treatment typically does not last long enough to comply with the 4 to 9 months of maintenance therapy recommended in national treat-

ment guidelines.[73] Navarro and colleagues examined drug discontinuation rates and reported that about two thirds of all patients on SSRI therapy discontinue therapy within 6 months, while more than 90% discontinue by 1 year.[63] In both HMO models, fluoxetine was associated with lower rates of discontinuation compared with paroxetine and sertraline, but this finding may be because the latter 2 SSRIs were relatively new to the market when this study was conducted.

According to the study by Thompson and colleagues on SSRI cost by pattern of use, duration of therapy is inversely related to overall treatment costs.[64] This analysis found that the mean overall treatment cost for those in the early discontinuation group (no more than 60 days of therapy) was $5610 during the follow-up period, second only to those in the switching/augmentation group ($7590). It is important to consider that these results are based almost entirely on utilization of fluoxetine.

Russell et al reported longer mean duration of therapy with fluoxetine (192 days) compared with paroxetine (157 days) and sertraline (166 days), but longer duration of therapy did not contribute to lower overall treatment costs with fluoxetine in this study.[69] This finding is different from that of the large-scale trial funded by the Food and Drug Administration, which found paroxetine to have the longest mean duration of therapy (103 days), followed by fluoxetine (90 days) and sertraline (69 days).[31] In the Russell et al study, fluoxetine was associated with the highest pharmaceutical and total healthcare costs because of the more frequent need for multitablet therapy.[69]

Further research is recommended to determine the impact of duration of therapy on depression-related treatment costs and to address factors that contribute to the perception that fluoxetine is associated with a longer duration of therapy than other SSRIs. For example, research is needed to investigate whether differences in length of therapy are related to the fact that SSRIs that followed fluoxetine to the market may be used frequently as second-line therapy in patients who did not respond to fluoxetine. These patients may have shorter drug trials with the second SSRI if a response is not evident within a few weeks.

··· COMORBID PSYCHIATRIC ILLNESS ···

Assessment of the overall impact of depression treatment must consider the high rate of psychiatric comorbidity. Patients with depression are more likely to have an anxiety disorder (eg, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder) than they are to experience depressive symptoms alone.[8] The lifetime prevalence of anxiety states, including panic disorder and phobias, is 25%, with an even higher prevalence in women (30.5%).[8] According to recent reports, 60% to 90% of patients with depression have comorbid psychiatric illnesses.[34,74] Similarly, about half to two thirds of patients with various anxiety states will also exhibit symptoms of depression.[16,75-77] These patients with comorbid illness have significantly worse symptoms, poorer prognosis and psychosocial functioning, and greater risk of attempting suicide than patients with depression alone.[34,74,78,79] The high rate of comorbidity among psychiatric illnesses indicates the need for safe and convenient interventions that have broad-based efficacy across multiple indications.

Because the SSRIs exhibit broad efficacy across multiple psychiatric indications, they represent alternative and viable monotherapeutic agents in patients with depression and comorbid anxiety disorders. The improved adverse effect profile and reduced potential for overdose-related toxicities with the SSRIs compared with older antidepressant classes indicate that these agents may be the treatment of choice for depression with comorbid anxiety.[80] Data comparing the overall treatment cost of the SSRIs versus that of the TCAs in patients with anxiety disorders or patients with comorbid psychiatric disease are not as extensive as in the area of depression. However, recent reviews suggest that such comparisons of these 2 drug classes would produce results similar to those in studies of depression because of the similar etiology of depression and anxiety disorders (serotonin dysfunction), the high rate of comorbidity between the conditions, and the high response rate to SSRI therapy.[81,82]

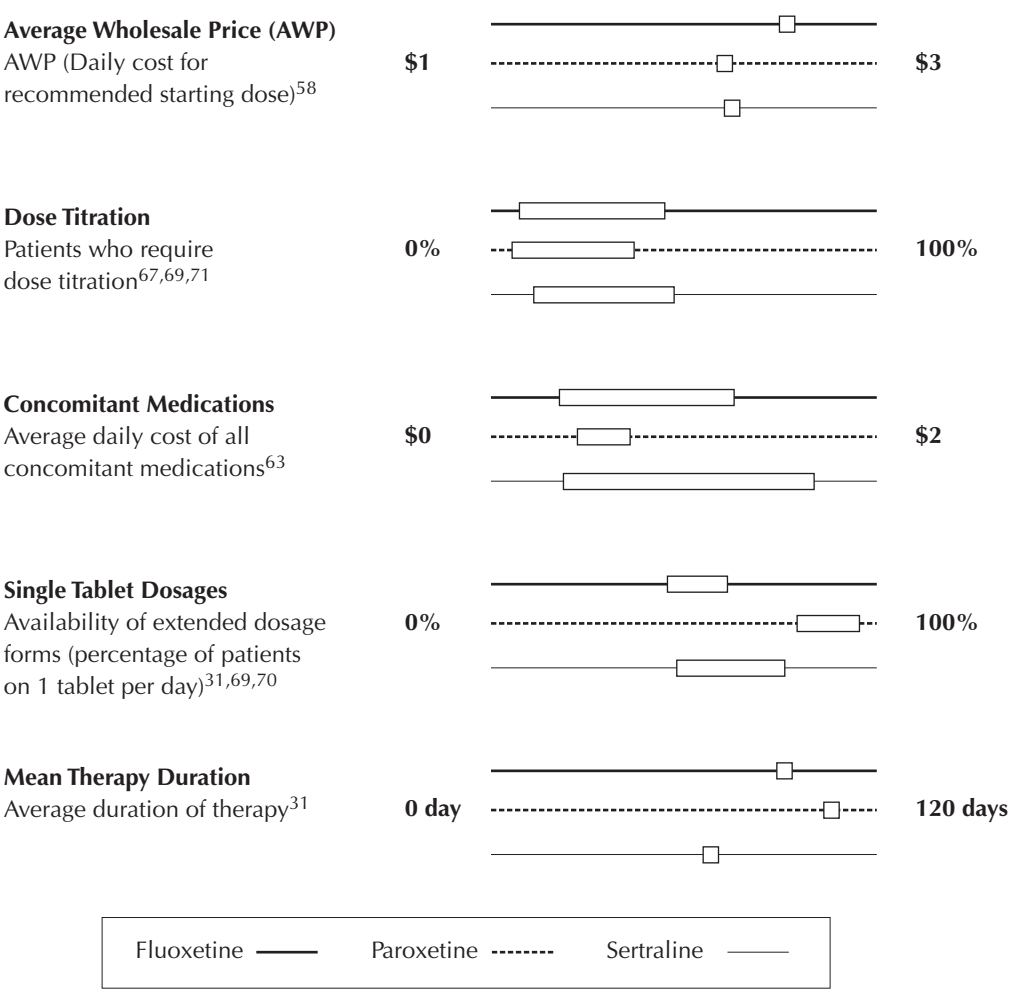
··· SUMMARY ···

Antidepressant therapy with SSRIs has been shown to be more cost effective than treatment with TCAs when overall healthcare utilization and expenses are considered. The SSRIs are now widely used as first-line therapy because they are safer and easier to administer than the TCAs, which dramatically improves the management of patients with depression. Treatment guidelines endorse the use of SSRIs as first-line treatment of depression, particu-

larly for patients who may not be able to tolerate the adverse effects associated with other antidepressants. The SSRIs also are recommended as first-line treatment of other psychiatric illnesses, such as panic disorder.[83]

Because well-designed, comprehensive pharmacoeconomic studies within the SSRI class are few, analysis of the cost effectiveness of the SSRIs may be based on a number of key factors: drug acquisition cost, use of concomitant medications, dose titration and dose stratification, and duration of therapy (**Figure 4**). A report on AWP indicates that paroxetine and sertraline have the lowest acquisition costs among the leading SSRIs. The percentage of patients on concomitant drug therapy may vary by healthcare plan, and the costs are typically minimal because most agents used with SSRIs are available generically. One study that reported costs for concomitant anxiolytic and hypnotic therapy showed that fluoxetine and paroxetine are associated with lower costs for concomitant medications. Dose titration has been shown to be the most important predictor of medical visits for patients receiving SSRI therapy. Paroxetine is associated with the lowest incidence of dose titration, whereas recent data suggest titration rates with fluoxetine and sertraline are similar. Paroxetine therapy is most likely to be maintained with a single tablet, followed by sertraline therapy. For all 3 SSRIs, duration of therapy is shorter than recommended by national treatment guidelines, and this topic warrants further study. Data from a large-scale study also show an inverse relationship between SSRI use in general and inpatient mental health

Figure 4. Trends for Cost Drivers of Selective Serotonin Reuptake Inhibitor Therapy



services, indicating the need for analysis of economic outcomes in this setting.

Further research is needed to examine the cost effectiveness of SSRI utilization for the treatment of depression and other psychiatric illnesses in terms of overall healthcare utilization and expenditures, similar to the comparison studies of SSRI and TCA therapy.

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