Selective Serotonin Reuptake Inhibitors: A Class Review

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OVERVIEW

Many changes and therapeutic advances have occurred in the treatment of depression in recent years, most notably the availability of the selective serotonin reuptake inhibitor (SSRI) class of agents, followed by the introduction of escitalopram oxalate (Lexapro™, Forest), the first agent in what is known as the “second generation” of SSRIs. However, because of the higher acquisition cost of SSRIs, compared with earlier antidepressants, managed care plans have begun to implement cost-containment strategies for these agents. As a result, P&T committee members are being asked not only to review efficacy and safety data but also to focus on available pharmacoeconomic data for this class of drugs.

Therefore, in addition to acquisition costs, issues relating to the onset of action, adverse drug events (ADEs), potential drug–drug interactions, and rates of patient discontinuation of treatment, P&T committees must consider expenses when selecting antidepressants for inclusion in the formulary and when determining the level of reimbursement for individual products.

Compared with the first-generation SSRIs, escitalopram, which was developed with the use of isomer technology, is associated with a more rapid onset of action, a more favorable ADE profile, fewer drug interactions, and thus a lower rate of therapy discontinuation. These clinical features result from isolating the S-enantiomer of citalopram hydrobromide (Celexa™, Forest). The isolation process renders escitalopram more selective for serotonin and thereby eliminates the undesirable effects that exist with the racemic compound, a mixture of “optically active” compounds that is not optically active itself. (Material is optically active if it preferentially absorbs or affects the polarization of light passing through it.)

The following topics are emphasized in this review:

• the epidemiology and economics of depression
• disease-management topics, including comorbidities and patient adherence to antidepressant treatment regimens
• ADE and pharmacokinetic profiles of the first-generation SSRIs and how individual differences among these drugs influence treatment selection
• the first second-generation SSRI, escitalopram

Epidemiology and the Economic Impact of Depression

Depression is a serious public health problem that has a significant impact on patients, their families, and health care providers. According to the World Health Organization, depression is a leading cause of disability worldwide. Epidemiologic studies suggest that in any 30-day interval, between 2% and 5% of the U.S. population experience an episode of major depressive disorder. In addition, the lifetime probability of experiencing a major depressive episode has been estimated to be as high as 17%.

Depression has profound social and economic consequences. In an economic study published in 1993, Greenberg et al. found that the total cost of depression in 1990 was $43.7 billion—$12.4 billion in direct costs, $23.8 billion in excess absenteeism and loss of worker productivity, and $7.5 billion in suicide-related lost earnings. Once identified, however, depression can almost always be successfully treated.

Antidepressants have been studied extensively in clinical trials and have been found to be efficacious in approximately 70% of patients. The efficacy of individual antidepressant medications is generally comparable between and within classes. An Agency for Health Care Policy and Research Practice Guidelines meta-analysis found virtually equivalent efficacy among different antidepressant medications but distinct variations in the tolerability profiles of individual SSRIs.

The success of treatment depends upon patient persistence (with patients continuing therapy for the entire length of time, from beginning to end) and adherence (the extent to which patients take the doses as prescribed during the therapeutic time frame). Major differences in adherence rates exist between antidepressants, primarily as a result of intolerable side effects and inconvenient dosing. Consequently, it is important to select an antidepressant according to its ADE, safety, and tolerability profiles and its suitability to the individual patient. Antidepressant medications with fewer side effects and less complex dosing regimens appear to be associated with better adherence rates.

The Challenges of Managed Care

The management of depression has become an important issue to managed care organizations (MCOs) because a diagnosis of depression has been linked to increased utilization of medical services and increased medical costs.

Utilization of Services

A three-year study among primary care patients with a high usage of services at a large health maintenance organization (HMO) found that a diagnosis of depression was associated with an increase of $1,498 in medical costs per patient. The study identified depressed patients whose use of services was sufficiently high that it would be possible to predict a cost offset by treating their depression for one year. Of these

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Depression and Coexisting Illness
Treatting depression in patients with coexisting medical illnesses is a particularly important challenge to MCOs. Up to 57% of patients commonly encountered in the primary care setting have depression and concomitant illness. Their tolerance of antidepressant medications differs from that of patients without concomitant illness: their office visits are more frequent, their hospital stays are longer, their compliance with treatment is poor, and their medical costs are higher.

In a study conducted at a large HMO, the annual health care costs for 6,257 primary care patients with a diagnosis of depression were higher ($4,246) than those for 6,257 non-depressed primary care patients ($2,371) ($ < .001), and their costs were increased for every category of care (primary care, medical specialty, medical inpatient, pharmacy, and laboratory). Many studies have suggested that treating depression in patients with comorbidities improves quality of life and helps to reduce the overall cost of care.

ACCESS TO ANTIDEPRESSANT THERAPY
Access to antidepressant medications can vary dramatically. Several studies have been conducted to identify predictors of diagnosis, the use of pharmacotherapy, and the use of the SSRIs. Sociological influences include patient and physician characteristics and their interaction with the health care system.

Utilizing data from the 1998 National Ambulatory Medical Care Survey (NAMCS), Sleath and Shih found that insured patients were twice as likely to receive antidepressant therapy. Patients with depression as their first diagnosis were much more likely to receive a prescription for an antidepressant. The patient’s age also affected physician-prescribing behavior; patients 18 to 34 years of age were more likely to receive an SSRI ($ < .1) than patients aged 65 or older. It is worth noting that patients whose visits were paid for under a capitation system of an HMO were four times more likely to receive a non-SSRI ($ < .1).

These data support the 1998 findings of Sclar et al. After analyzing data from the 1995 NAMCS, these investigators found that of the more than 18 million office-based visits that resulted in a diagnosis of depression, more than 50% of the patients (56.2%) self-reported that depression was the primary reason for the office visit, more than one third (67.5%) received antidepressant therapy, and almost half (48.4%) received an SSRI or a serotonin/norepinephrine reuptake inhibitor (SNRI). Female patients and patients younger than age 50 were more likely to receive an SSRI or an SNRI. The likelihood of receiving a prescription for these newer therapeutic options increased by 46% when the patients had private insurance.

In view of the fact that patients with depression sometimes have higher annual health care costs and a lower quality of life, and because the cost of newer therapies might be offset by reductions in the use of health care resources, the economic and other barriers to antidepressant therapy need to be addressed. Access to these medications in general, and the newer class of SSRIs in particular, may provide better treatment outcomes while still offering the most cost-effective care.

RATIONALE FOR THE DEVELOPMENT OF SSRIs
The discovery of the SSRI class of antidepressants is the result of research that was aimed at finding drugs that were as effective as the tricyclic antidepressants (TCAs) but that posed fewer safety and tolerability problems. Treatment with TCAs, such as amitriptyline (various manufacturers), clomipramine (Anafranil®, Mallinckrodt), doxepin (Sinequan®, Pfizer), imipramine (Tofranil®, Mallinckrodt), and trimipramine (e.g., Surmontil®, Wyeth), has been associated with dosing problems that prevented patients from achieving adequate therapeutic levels of the drug and treatment-limiting side effects, a consequence of their noneffective activity. The SSRIs selectively and effectively block the reuptake of serotonin at central synapses, resulting in a potentiation of serotonergic neurotransmission.

In the U.S., the first-generation SSRIs—fluoxetine (Prozac®), Eli Lilly), paroxetine (Paxil®, GlaxoSmithKline), sertraline (Zoloft®, Pfizer), and citalopram (Celexa®, Forest)—are now considered first-line therapies for depression. The other first-generation SSRI, fluvoxamine maleate (Luvox®, Solvay), is approved in the U.S. only for obsessive-compulsive disorder (OCD) and is not included in this discussion.

Other antidepressant agents that block the uptake of both serotonin and norepinephrine (the SNRIs) have recently been developed. In this category, both venlafaxine (Effexor®, Wyeth) and mirtazapine (Remeron®, Organon) have demonstrated superior efficacy to placebo and comparable efficacy to TCAs. Venlafaxine has an ADE profile similar to that of the SSRIs, but it may also induce hypertension. In placebo-controlled clinical trials, venlafaxine was associated with a higher rate of nausea (31%) compared with fluoxetine (21%), paroxetine (22%), sertraline (26%), and citalopram (15%).

In approximately 50 randomized, placebo-controlled trials, SSRIs were as effective as TCAs in the treatment of major depressive disorder. In other studies, SSRIs led to enhanced patient adherence to antidepressant therapy.

In an analysis of the duration of antidepressant therapy for 119 HMO enrollees who began antidepressant therapy, Katon et al. found that, over a six-month period, only 20% of patients who had been prescribed TCAs complied with therapy (i.e., filled four or more prescriptions), compared with 34% of patients with prescriptions for SSRIs and other reuptake inhibitors.

In a study of patients being treated by primary care physicians and psychiatrists in a large staff-model HMO, Simon et al. found that 75% of patients who were taking SSRIs were
more likely to continue treatment beyond one month, compared with 54% of patients who were taking TCAs. In the same study, 51% of patients in the SSRI group adhered to therapy sufficiently to reach an adequate therapeutic daily dose, compared with only 26% in the TCA group.

Analyses of dosages and refills from large prescription databases in North America and Europe have consistently found that patients taking SSRIs were less likely to discontinue treatment and were more likely to receive effective therapeutic doses.8

In general, no significant differences in efficacy among the currently available first-generation SSRIs have been observed,6 although the incidence of frequent ADEs among the SSRIs does vary.8

Dosing regimens, daily costs, and indications for the SSRIs are summarized in Table 1.

**SSRIs: UNIQUE AGENTS WITHIN A CLASS**

Each drug in the SSRI class has a unique pharmacological and ADE profile. These differences may be important considerations for all patients receiving SSRIs and, as mentioned earlier, are of particular concern for patients who have coexisting medical conditions and who may also be receiving multiple medications, because polypharmacy can increase the potential for drug–drug interactions.8 Knowledge of the differences that exist among the SSRIs with respect to their safety and tolerability can aid in the selection of the most beneficial treatment.

The ADEs reported during treatment with SSRIs have been found to be dose-related and, to some degree, predictable from the pharmacology of the compounds. These side effects are usually mild and improve with continued treatment.6,8 Pharmacoeconomic studies comparing TCAs with SSRIs suggest that a knowledge of the clinical differences between the SSRIs can translate into significantly improved economic outcomes. A successful clinical result—measured in tolerability, safety, and patients’ adherence to therapy—leads to a reduced economic burden on both patients and health care providers.8

**ANTIDEPRESSANT ADVERSE DRUG EVENT PROFILES**

ADEs resulting from antidepressant therapy can have a major effect on patients’ adherence to therapy and continuation of treatment. ADEs associated with SSRIs (e.g., gastrointestinal and psychiatric changes, sleep disturbances, weight gain or loss, and sexual dysfunction)8 are dose-related. They may be minimized with slow titration, and they tend to diminish over time.6 However, differences in tolerability observed among the SSRIs may be clinically relevant in specific patient populations and may affect treatment success. The most significant ADEs in patients being treated for major depressive disorder are summarized next.

**Anticholinergic Effects**

Paroxetine, like the TCAs desipramine (Norpramin®, Aventis) and imipramine, has an in vitro affinity for the muscarinic cholinergic receptor. As a result, paroxetine causes a higher rate of anticholinergic effects, such as dry mouth, constipation, and cognitive disruption, compared with other SSRIs. These effects may be particularly difficult to tolerate for elderly or concomitantly medically ill patients.19

**Agitation and Anxiety**

Agitation, anxiety, and insomnia may occur more frequently with some SSRIs and sometimes prevent an adequate duration of treatment. For example, in a controlled, randomized trial of fluoxetine and sertraline, fluoxetine-treated patients with major depressive disorder experienced a higher incidence of these ADEs than did patients receiving sertraline.26 Sertraline was

### Table 1  The First-Generation Selective Serotonin Reuptake Inhibitors

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Dose Range/ Frequency</th>
<th>Average Wholesale Price per Day†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Celexa™*</td>
<td>Forest</td>
<td>Depression</td>
<td>20–60 mg q.d.</td>
<td>$2.22–$2.42</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac®#</td>
<td>Eli Lilly</td>
<td>Depression, OCD, bulimia nervosa, panic disorder</td>
<td>20–80 mg q.d.</td>
<td>$3.11–$12.46</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Generic®‡</td>
<td>Various</td>
<td>Depression, OCD, bulimia nervosa</td>
<td>20–80 mg q.d.</td>
<td>$1.55–$6.40</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil®#</td>
<td>GlaxoSmithKline</td>
<td>Depression, OCD, panic disorder, SAD, GAD, PTSD</td>
<td>20–50 mg q.d.</td>
<td>$2.71–$5.42</td>
</tr>
<tr>
<td>Paroxetine CR*</td>
<td>Paxil® CR*</td>
<td>GlaxoSmithKline</td>
<td>Depression, panic disorder, SAD, PMDD, PTSD</td>
<td>25 mg q.d.</td>
<td>$2.67†</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft®#</td>
<td>Pfizer</td>
<td>Depression, OCD, panic disorder, PMDD, PTSD, SAD</td>
<td>50–200 mg q.d./b.i.d.</td>
<td>$2.52–$5.04</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = post-traumatic stress disorder; q.d. = once daily; SAD = social anxiety disorder.

* Data from package inserts.22–35,47
† Data from Valuck RJ. Round table discussion presented at the third annual P&T Society meeting, May 28, 2003, Chicago.45
‡ Data from Hamer AM. Available at www.cascadeseast.org.46
considered to be better tolerated overall. Only 9.6% of sertraline-treated patients discontinued therapy as a result of treatment failure, but 19.6% of fluoxetine-treated patients stopped treatment.

**Body Weight**

The SSRIs also vary in their effect on patients’ weight. Sertraline is generally associated with a small degree of weight loss in the acute phase of treatment, whereas paroxetine caused weight gain after long-term treatment. Fluoxetine has the most potent appetite-suppressing effects in the short term and produces a greater degree of weight loss than paroxetine, sertraline, or citalopram.8

Although weight gain might be stressful to some patients and might cause them to discontinue therapy, weight loss in elderly patients can be particularly problematic. Major depressive disorder and concomitant medical illness are frequent in this age group, and weight loss can have a deleterious effect on general health. For older patients, the choice of an antidepressant that is not generally associated with weight change may be beneficial.8

**Sexual Dysfunction**

All antidepressants affect sexual function, either negatively, as a result of ADEs, or positively, as a result of therapeutic success. Treatment with SSRIs has been associated with sexual dysfunction, especially delayed ejaculation in men and orgasmic dysfunction in women. The type of sexual dysfunction varies according to the specific SSRI, probably because of the different pharmacological and pharmacokinetic properties, and the effects appear to be dose-related.

Of the available SSRIs, paroxetine appears to cause the highest rate of sexual dysfunction. In other comparative studies, sexual dysfunction occurred more frequently in men receiving fluoxetine than in those receiving sertraline.

Citalopram has been associated with loss of libido and may be associated with a relatively higher level of sexual dysfunction compared with sertraline. These side effects may have a pronounced impact on patients’ adherence to treatment.

**DISTINCT PHARMACOKINETIC PROFILES**

In addition to the various ADEs associated with SSRIs, clinicians must consider the distinct pharmacokinetic profiles when selecting among antidepressants with equal efficacy, especially for patients with coexisting disease and elderly patients. Practical considerations include:

- the drug’s elimination half-life and the presence of active metabolites.
- whether the drug’s pharmacokinetic properties are linear or nonlinear.
- withdrawal reactions upon interruption or discontinuation of therapy.
- the potential of the treatment to cause clinically significant drug–drug interactions (perhaps the most important consideration).

These characteristics are discussed next and are summarized in Table 2.

**Half-Life**

The half-life of a drug is the time required to achieve steady-state plasma concentrations (i.e., to metabolize half the dose and lower blood concentrations by 50%). Half-life can be used to estimate how long it will take to clear a drug from the body after treatment is discontinued. The half-life of both the parent compound and all active metabolites can be an important consideration during selection of a treatment regimen for patients with depression and comorbidities; a shorter half-life avoids the dangers associated with drug accumulation and the need for extended washout periods after discontinuation of treatment. Fluoxetine, for example, has a half-life of six days. Unlike the other SSRIs, it has an active metabolite (norfluoxetine) with a

### Table 2  Pharmacokinetics: How the First-Generation SSRIs Compare

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sertraline*</th>
<th>Fluoxetine*</th>
<th>Paroxetine*</th>
<th>Citalopram*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life†</td>
<td>26 hours</td>
<td>1–3 days acute</td>
<td>10 hours acute</td>
<td>35 hours</td>
</tr>
<tr>
<td>Linear pharmacokinetics/</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>dose-proportionality plasma levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein-bound (%)</td>
<td>98%</td>
<td>94.5%</td>
<td>95%</td>
<td>80%</td>
</tr>
<tr>
<td>Absorption affected by food</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Isoenzyme inhibition41</td>
<td>CYP2D6 ++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>CYP1A2 +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>CYP3A +</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CYP2C19 + to ++</td>
<td>+ to ++</td>
<td>+ to ++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>CYP2C9 +</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

* Data from package inserts.22–25  
† Data from Goodnick PJ, Goldstein BJ. J Psychopharmacol 1998;12(Suppl B):S5–S20.19  
‡ Data from Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. J Clin Psychiatry 1998;59(Suppl 15):19–27.41  
Key: 0 = minimal inhibition; + = mild inhibition, ++ = moderate inhibition, +++ = substantial inhibition.
half-life of 14 to 21 days. It may therefore take three or four weeks for patients to achieve steady-state concentrations after beginning fluoxetine therapy or changing dosages.

In contrast, sertraline, paroxetine, and citalopram have shorter half-lives of approximately 10 to 33 hours, and steady-state concentrations—and therapeutic effect—are reached much more rapidly. Antidepressants with relatively short (intermediate) half-lives are especially desirable for patients with multiple comorbidities and complex, multiple-drug regimens because they allow for once-daily dosing. A short half-life enables physicians to switch more rapidly and safely to an alternative antidepressant if treatment fails or if unfavorable drug reactions occur.

### Dose Proportionality and Linear/Nonlinear Pharmacokinetics

One of the most important differences to note among the SSRIs is whether their pharmacokinetic properties are linear or nonlinear. Sertraline and citalopram follow linear pharmacokinetics (i.e., plasma concentrations of the drugs are proportional to the daily dose administered and, therefore, predictable). Fluoxetine and paroxetine demonstrate nonlinear pharmacokinetics (i.e., higher doses may produce much greater increases in plasma drug concentrations than would otherwise be expected). Thus, increasing the dose of paroxetine or fluoxetine can result in disproportionate and unpredictable increases in plasma levels, half-lives, and ADEs. Titration of fluoxetine and paroxetine doses may therefore be more difficult than with sertraline and citalopram.

### Withdrawal Reactions

Interruptions in antidepressant treatment occur for many reasons, such as periods of hospitalization or the effects of illness or its treatment. Interrupting or withdrawing from SSRI treatment can result in significant adverse reactions, including anxiety, nausea, dizziness, paresthesia, tremor, and palpitations, depending on the agent.

Withdrawal reactions appear to be associated with SSRI plasma concentrations that decrease so quickly that the central nervous system does not have time to adjust. Among SSRIs, paroxetine, with its short half-life, clearly stands out from the group in its propensity to cause discontinuation reactions. However, because both sertraline and citalopram have linear pharmacokinetics, their half-lives are not affected by plasma concentrations and the rapid decline in drug levels associated with paroxetine does not occur. Withdrawal reactions and lengthy washout periods can be avoided if patients take an agent with an intermediate half-life (e.g., sertraline or citalopram).

### Drug Interactions

Perhaps the most important consideration in selecting an antidepressant for a patient who may already be taking multiple medications is the potential for clinically significant drug–drug interactions. The potential of individual SSRIs to produce drug interactions is influenced by their effects on cytochrome P450 (CYP450) enzymes involved in the metabolism of a wide range of drugs. As shown in Table 2, the potential for SSRIs to interact with other drugs metabolized by the CYP enzyme system is greatest for fluoxetine and paroxetine and least for citalopram.

As an example, fluoxetine and paroxetine are potent inhibitors of CYP2D6, whereas sertraline and citalopram have minimal effects on the enzyme. The potential for CYP2D6 inhibition becomes critical when therapy must be selected for patients with cardiovascular disease, because CYP2D6 is involved in the metabolism of the following cardiac agents:

- beta blockers, such as propranolol (e.g., Inderal®, Wyeth; InnoPran®, Reliant) and metoprolol (e.g., Lopressor®, Novartis; Toprol®, AstraZeneca)
- type IC antiarrhythmic agents such as flecainide (TamboCor®, 3M) and encainide (Enkaid®, Bristol-Myers Squibb)
- verapamil (e.g., Calan®, Pfizer)

CYP2D6 inhibition by fluoxetine or paroxetine may result in dangerously high plasma levels of these drugs. As a result, sertraline would be preferable for cardiac patients taking beta blockers or type IC antiarrhythmic agents.

### Pharmacoeconomic Studies

Numerous pharmacoeconomic studies have been conducted to determine whether patients show sufficient improvement after taking SSRIs, instead of TCAs, to justify their higher costs. One prospective, randomized trial compared clinical outcomes and treatment costs for patients in a staff-model HMO who were initially prescribed an SSRI or a TCA. Patients with initial prescriptions of fluoxetine experienced fewer side effects and lower rates of medication switching and were more likely to reach adequate dosing levels than patients who began with prescriptions for TCAs. Total costs for care over six months were equal for each group. The higher cost of the fluoxetine therapy was balanced by fewer outpatient and inpatient costs.

In a study at a large HMO, McFarland compared the TCA imipramine with the SSRI paroxetine in the primary care setting. The investigators found that the increased acquisition cost of paroxetine was offset by the greater direct expenditures associated with imipramine therapy, including primary care labor costs (repeated clinical and pharmacy visits to adjust dosage) and repeated maintenance visits to ensure compliance and to monitor side effects.

Although studies comparing TCAs and SSRIs have generally shown that the higher acquisition costs of SSRIs are offset by decreased health care service utilization and other economic benefits associated with improved compliance and tolerability, pharmacoeconomic studies comparing SSRIs have yielded conflicting results on the specific benefits for individual agents.

Crown et al. compared initial treatment with sertraline, paroxetine, and fluoxetine. Although fluoxetine had the highest predicted cost for antidepressant treatment, there were no statistically significant differences between the three treatment groups in total direct health care costs over the two-year evaluation period (P < .05). The fluoxetine patients were significantly more likely than the sertraline or paroxetine patients to achieve a usage pattern that was consistent with treatment
guidelines for depressive disorder \( (P < .05) \). In addition, depression-related expenditures, other mental health expenditures, and non–mental health care expenditures showed no significant differences across treatment groups \( (P < .05) \).

Sclar et al. designed a study to compare direct health service expenditures for the treatment of depression among \( 744 \) patients enrolled in an HMO.\(^3\) One of three SSRIs was prescribed: fluoxetine, paroxetine, or sertraline. One year after paroxetine treatment began, per capita health service use increased by $284.68 \( (P \leq .05) \) compared with fluoxetine. In contrast, sertraline treatment increased total per capita health service use by $315.96 \( (P \leq .05) \) compared with fluoxetine. However, economic comparisons of paroxetine and sertraline demonstrated no significant differences in expenditures for the health services examined.

Other studies reported economic benefits for sertraline based primarily on lower acquisition costs and tablet-splitting practices.

Singletary et al.\(^3\) studied the advantages and disadvantages of individual SSRIs at the Denver Veterans Affairs Medical Center. They found that the average daily cost to the medical center was $2.01 for fluoxetine, $1.18 for sertraline, and $1.24 for paroxetine. Switching from fluoxetine to sertraline resulted in a drug acquisition cost difference of $0.83 per patient per day between fluoxetine and sertraline, or a drug cost reduction of $302,674 per year.

A study by Nurenberg et al.\(^3\) was specifically designed to determine the average cost per day of individual SSRIs to help guide treatment choices based on this factor alone. This study, which enrolled 2,779 patients at an outpatient psychiatric teaching clinic, analyzed acquisition costs for the three most frequently prescribed SSRIs. The average cost per day, as determined by dose distribution, was $1.79 for fluoxetine, $1.41 for paroxetine, and $1.21 for sertraline. Between the three groups, there were no differences in the switch rates or the clinical outcomes, factors that can often lead to increased health care costs.

It is important to keep in mind that these pharmacoeconomic studies were performed before fluoxetine was available in a generic form (August 2001).\(^3\) It is anticipated that the reduced price of generic fluoxetine will reduce the acquisition costs for HMOs and other health plans and thus alter the breakdown of total direct health care costs among the SSRIs.

Once-weekly fluoxetine is now available, although not in a generic form; it is indicated only for patients who have been receiving three months of daily fluoxetine and whose weekly dosage requirements do not exceed 90 mg.\(^3\)

Thus, despite the unique characteristics of SSRIs and differences in their tolerability, pharmacoeconomic studies to date have not demonstrated a cost benefit for any single SSRI. However, no one study has compared all available first-generation agents. Most significant is the general absence of citalopram and the second-generation SSRI escitalopram from these investigations. Citalopram, and to a greater extent escitalopram, appear to have a low ADE profile and a benign pharmacokinetic profile—two factors that have been shown to reduce patient switch rates; the frequency of discontinuation; repeated office visits; and, by extension, the overall cost of treatment.

### ESCITALOPRAM

#### Rationale for Development

From the preceding discussion, it is evident that no single agent appears to share all the characteristics of the ideal antidepressant drug (i.e., rapid onset of action, a short half-life, minimal discontinuation effects, an absence of ADEs, negligible drug interactions, a broad spectrum of activity, and low cost). Efforts to develop better antidepressants are ongoing and are directed at devising a drug that would improve upon the existing SSRIs in terms of safety, tolerability, and efficacy, which in turn would result in an improved pharmacoeconomic profile. The most recent efforts have been aimed at refining the active isomers of existing drugs.

In this regard, chirality \( (\) the characteristic of a molecule that causes it not to be identical to or not to coincide with its mirror image) may provide a way to improve upon the SSRI class of antidepressants. Investigators suggest that if all therapeutic activity of a racemic compound resides in one isomer, that single isomer would be more potent and selective than its mirror image.\(^3\) Clinical development of that single isomer may thus result in a compound whose therapeutic index is superior to that of the less active isomer, presumably because of its higher potency and selectivity and its lower ADE profile.\(^3\)

#### Pharmacokinetics

Escitalopram is the S-isomer of the racemic compound citalopram. The therapeutic efficacy of citalopram resides almost exclusively in the S-isomer.\(^3\)\(^,\)\(^3\)\) Escitalopram exhibits higher selectivity for the human serotonin transporter relative to the human noradrenaline or dopamine transporters than any currently available SSRI, including citalopram.\(^3\)

A pooled analysis of placebo-controlled trials evaluating the effectiveness of escitalopram and citalopram suggests that escitalopram offers several advantages over citalopram, a first-generation SSRI.\(^3\) Although both escitalopram and citalopram improved depression more than placebo did, escitalopram showed statistically significant improvement over citalopram when compared with placebo. It was statistically significantly superior to citalopram in improving patients’ scores on the Montgomery Asberg Depression Rating Scale (MADRS).\(^3\)

Escitalopram is a more potent and selective inhibitor of serotonin reuptake than citalopram, and escitalopram therapy has consistently brought about a greater reduction of the symptoms of depression compared with citalopram at equivalent doses.\(^3\)

Escitalopram seems to offer a less complicated pharmacokinetic profile and better tolerability because the R-citalopram isomer has been removed. Like citalopram or its racemate, escitalopram has minimal interaction with the CYP450 enzyme system,\(^3\) which is responsible for the metabolism of many drugs, including antidepressants. Several clinically important pharmacokinetic drug interactions result as a consequence of CYP450 inhibition and the ensuing lack of metabolic clearance.\(^3\)\(^,\)\(^3\)\) Accurate knowledge of the inhibitory effect of a particular antidepressant on the CYP450 enzyme pathway will assist health care professionals who must make treatment choices.\(^3\)

Table 2 (see page 237) shows the pharmacokinetic profile of the first-generation SSRIs. Citalopram displays consistently
minimal-to-mild inhibition in a variety of CYP450 enzyme pathways, compared with other first-generation SSRIs, some of which display substantial inhibition.

Table 3 shows the pharmacokinetic profile for escitalopram. CYP450 enzyme inhibition for escitalopram is minimal to weak for each significant pathway tested. Pharmacological studies have demonstrated that escitalopram is unlikely to be involved in clinically significant drug–drug interactions.42

Clinical Trials
The safety and efficacy of escitalopram in the treatment of depression have been evaluated systematically in randomized, double-blind, placebo-controlled, eight-week trials. The first three reports derived from these studies are described as follows.

The Wade Study: Escitalopram 10 mg/day vs. Placebo in a Primary Care Setting
Wade et al. conducted a study of primary care outpatients with a major depressive episode, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth revised edition (DSM IV).38 Patients’ baseline MADRS total scores ranged between 22 and 40. A total of 380 patients were randomly selected to receive escitalopram 10 mg/day (n = 191) or placebo (n = 189). After a one-week, single-blind placebo lead-in, patients received eight weeks of double-blind treatment. The primary efficacy measure was changed from the baseline value on the MADRS. Other clinical efficacy measures included the Clinical Global Impression of Severity of Illness (CGI-S) and the Clinical Global Impression of Improvement (CGI-I).

Escitalopram 10 mg/day demonstrated consistent antidepressant efficacy throughout the study. In efficacy analyses performed each week, the antidepressant effect of escitalopram was significantly greater than that of placebo (P < .05) as early as the first week for CGI-I, the second week for MADRS, and the third week for CGI-S. These scores were maintained throughout the study period. Nausea was the only ADE reported by more escitalopram-treated patients than placebo-treated patients, although it was infrequent and transient. The authors concluded that escitalopram at a fixed dose of 10 mg/day was effective in treating major depressive disorder and that the drug’s excellent tolerability and efficacy made it an ideal first-choice line of treatment for depression in primary care.38

The Burke Study: A Fixed-Dose Trial
In this fixed-dose multimember trial conducted by Burke et al.,35 491 outpatients with ongoing DSM-IV major depression were randomly assigned to receive placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, or citalopram 40 mg/day for eight weeks after a one-week, single-blind, placebo lead-in phase. Clinical responses were assessed by MADRS scores, the 24-item Hamilton Rating Scale for Depression (HAM-D), the CGI scales, and the Hamilton Rating Scale for Anxiety (HAM-A) as well as patient-rated quality-of-life scales.

Compared with placebo, both the 10- and 20-mg doses of escitalopram produced significant improvement at the study endpoint on all measures of depression. Within one week of double-blind treatment, the researchers observed a significant difference in the effectiveness of escitalopram versus placebo and significant improvement in depressive symptoms with citalopram compared with placebo.

At the study endpoint, escitalopram 10 mg/day was at least as effective as citalopram 40 mg/day. Anxiety symptoms were also significantly improved with escitalopram compared with placebo. The incidence of discontinuation resulting from ADEs for the group taking escitalopram 10 mg/day was similar to the group taking placebo (4.2% vs. 2.5%, respectively; P = .50). Discontinuation rates for the escitalopram group taking 20 mg/day (10.4%) and for the citalopram group taking 40 mg/day (8.8%) were also similar (P = .83).35

The Gorman Study: A Pooled Analysis of Placebo-Controlled Trials
Because no single escitalopram study was sufficiently powered to compare citalopram and escitalopram efficacy, Gorman et al. pooled data from three similarly designed, randomized trials of escitalopram (10–20 mg/day) and citalopram (20–40 mg/day).40 Two of the studies were flexible-dose trials, and one was a fixed-dose trial.

A total of 1,321 patients were included in the pooled intent-to-treat population, which included men and women 18 years of age or older who met criteria for a major depressive episode with a baseline MADRS score of 22 or higher. The medications in the fixed-dose study were titrated to full dose at the first week. Efficacy measures included changes from baseline scores in the MADRS and in the CGI-I. The changes from the baseline MADRS score regarding inner tension were used to measure improvement in associated symptoms of anxiety.40

Both citalopram and escitalopram therapy significantly alleviated depression and anxiety symptoms compared with placebo, with significantly more MADRS responders in the

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**Table 3 Escitalopram Profile**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Escitalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average price/day</td>
<td>$2.13–$2.23†</td>
</tr>
<tr>
<td>Dosage/frequency</td>
<td>10–20 mg once daily</td>
</tr>
<tr>
<td>Peak plasma levels</td>
<td>5 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>27–32 hours</td>
</tr>
<tr>
<td>Linear pharmacokinetics/</td>
<td></td>
</tr>
<tr>
<td>dose-proportionality</td>
<td>Yes</td>
</tr>
<tr>
<td>Protein-bound (%)</td>
<td>56%</td>
</tr>
<tr>
<td>Absorption affected by food</td>
<td>No</td>
</tr>
<tr>
<td>Dose adjustment for mild to moderate renal or hepatic impairment</td>
<td>None</td>
</tr>
<tr>
<td>Isoenzyme inhibition</td>
<td></td>
</tr>
<tr>
<td>CYP1A2</td>
<td>0‡</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>0</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>0</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>0</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>0</td>
</tr>
</tbody>
</table>

† Data from Valuck RJ. Round table discussion presented at the third annual P&T Society meeting, May 28, 2003, Chicago.
Key: 0 = minimal or weak inhibition.
escitalopram and citalopram treatment groups. Escitalopram was associated with statistically significant improvements in all efficacy measures versus placebo after one week of treatment, whereas citalopram treatment did not differ from placebo until the end of the fourth week (the CGI-I and MADRS item on inner tension) or the sixth week (MADRS). A statistically significant advantage of escitalopram treatment in relation to citalopram was observed at the fourth and sixth weeks.40

These data support the effectiveness of citalopram and escitalopram in the treatment of major depression but also suggest that escitalopram might have a faster onset of action and greater overall magnitude of effect than citalopram in improving symptoms of depression and anxiety.40

The Rapaport Study: Prevention of Relapse of Depression

A substantial risk of relapse is associated with the discontinuation of antidepressant therapy after the acute symptoms of a depressive episode resolve. It is widely recognized that an additional four to six months of continued treatment is needed to consolidate patient response and to prevent relapse.6,43

Rapaport et al. conducted a multicenter trial to determine whether escitalopram could help prevent a recurrence of depression.43 During the open-label phase of the trial, depressed outpatients who had previously completed eight weeks of randomized, double-blind continuation therapy with escitalopram, citalopram, or placebo received eight weeks of treatment with escitalopram 10 to 20 mg/day. During the double-blind phase, 274 responders from the open-label phase (MADRS scores 12 or higher) were randomly assigned to receive 36 weeks of treatment with either escitalopram (n = 181) or placebo (n = 93). Relapse was defined as a MADRS score of 22 or higher or withdrawal from the study because of a lack of therapeutic response.

The time to depression relapse was significantly longer, and the cumulative rate of relapse was significantly lower, in escitalopram-treated patients (26%) than in placebo-treated patients (40%).43 Continuing with escitalopram decreased the percentage of patients who met the DSM-IV criteria for depression (23%) compared with placebo (35%). The authors concluded that escitalopram 10 to 20 mg/day was effective in treating depression and in preventing relapse.43

The Burke Studies: Safety and Tolerability

The preparation of a single isomer from a drug that had been previously available only as a racemic mixture has resulted in alterations in the agent’s potency, efficacy, and tolerability.36 Numerous randomized, controlled trials have established the superior efficacy of escitalopram (the single isomer of citalopram) over the first-generation SSRIs in patients with major depressive disorder.

In addition to its improved efficacy, escitalopram offers better safety and tolerability than the first-generation SSRIs do in terms of decreased drug–drug interactions, serotonin selectivity, a less complex plasma concentration–effect relationship,36 and a reduced ADE profile as follows:35

- Owens et al.36 concluded that the ADE profile for citalopram was relatively benign and that the potential for drug–drug interactions was reduced, compared with other first-generation SSRIs.
- In their primary efficacy analysis, Wade et al.38 found 10 mg/day of escitalopram to be both clinically and statistically significantly superior to placebo in the treatment of depression, with a very good tolerability and efficacy in a wide range of depressed patients.
- Burke et al.35 demonstrated strong clinical support for the efficacy and tolerability of 10 mg/day or higher of escitalopram. Discontinuation rates attributed to ADEs were similar to those for placebo at both 10 and 20 mg/day, and analysis of laboratory tests, vital signs, body weight, and electrocardiographic parameters showed no clinically relevant changes from baseline values in patients receiving escitalopram.
- Although the most commonly observed ADEs in patients treated with escitalopram were insomnia, ejaculation disorder, nausea, increased sweating, fatigue, and somnolence, the percentage of patients experiencing these ADEs was similar to that of the placebo-treated patients, except for nausea (in 15% taking escitalopram vs. 7% taking placebo) and ejaculation disorder (in 9% taking escitalopram vs. fewer than 1% taking placebo).44

PHARMACOECONOMIC EVALUATION

A comparison study of escitalopram and the first-generation SSRIs is currently under way to determine whether the clinical advantages offered by escitalopram (i.e., effectiveness, low risk of drug–drug interactions, reduced ADEs, improved tolerability)—will translate into more cost-effective antidepressant treatment under real-world practice conditions. In this effort, the data from the package insert and those of other available generic and branded SSRIs will be evaluated.22–25,46,47

Key questions to be addressed include:

- whether fewer side effects will result.
- the occurrence of drug–drug interactions.
- the number of physician or emergency department visits among patients taking specific agents.
- the cost of treating each depressed patient successfully.
- the factors that affect depression-related expenditures over six months to one year.

As indicated from preliminary results of analyses of a large database of managed care claims, before escitalopram became available on the market, the primary factors driving cost included the following:

- whether the patient was receiving psychotherapy (if so, six-month costs were 73% higher)
- the type of drug initially prescribed (first-generation SSRIs cost 7% to 29% more than citalopram)
- the presence of comorbidities (each additional coexisting illness added 15% to costs)

These early results also showed that total health care costs in the six months after a diagnosis of depression were lowest for escitalopram. The full results of this study are eagerly anticipated.
CONCLUSION

Although SSRIs represent a clinically significant advance over earlier antidepressant medications, the first-generation SSRIs still fall short of the ideal antidepressant. The second-generation agent escitalopram, however, which is a more selective SSRI, offers considerable improvement. At present, no clear clinical or economic advantage has emerged for any one of the first-generation SSRIs.

Current guidelines recommend that treatment be tailored to the needs of patients according to the potential for drug interactions and ADEs. Recent investigations, however, suggest that refinement of existing drugs from their active isomers (e.g., with the realization of escitalopram from citalopram) might translate into improved clinical and economic benefits, bringing us closer to the ideal agent.

The potential benefits of the second-generation SSRIs, particularly single-isomer SSRIs such as escitalopram, include a reduction in the total dose necessary to achieve therapeutic effects, a faster onset of action, fewer ADEs and drug interactions, and an improved pharmacoeconomic profile. Additional well-controlled studies are needed to confirm these benefits.

Before recommending any antidepressant, physicians should refer to the full prescribing information.

REFERENCES

SSRIs: A Class Review


