

Diagnosis and Therapeutic Management of Depression: An Update in the Use of Selective Serotonin Reuptake Inhibitors (SSRIs)

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Learning Objectives

After completing this continuing education program, the pharmacist will be able to:

1. Discuss the economic impact that depression has on the United States.
2. Recognize the signs and symptoms of depression.
3. List the selective serotonin reuptake inhibitors (SSRIs) available in the United States for the treatment of depression and discuss their pharmacology and pharmacokinetics.
4. Identify the adverse reactions and drug interactions associated with SSRIs.
5. Compare and contrast the SSRIs used in the treatment of depression.
6. Discuss ways to improve the diagnosis and treatment of depression in the United States.

Abstract: Major depression is a very common disorder in the United States. Although effective treatment has been available for almost 40 years, it often goes underdiagnosed and, consequently, undertreated. It has been estimated that the annual cost of depression in the United States totals approximately \$43 billion. This figure includes the direct costs of medications and physician visits as well as indirect costs, such as loss of productivity in the workplace. Therefore, it is important to recognize the signs and symptoms of depression in order to treat the disease. The discovery of selective serotonin reuptake inhibitors (SSRIs) has had a major impact on the therapeutic management of depression. Five SSRIs are currently available in the United States market: citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. This review will focus on the recognition and diagnosis of depression as well as a comparison of the available SSRIs. The SSRIs have made an impact in the treatment of depression because of their favorable side effect profile, tolerability, and relative safety in overdose. Although the SSRIs have, essentially, the same pharmacology, their chemical structures are slightly different; thus, they differ slightly in their side effect profiles as well as their interactions with other medications. The selection of the appropriate SSRI should be based on the patient's

symptoms of depression, concurrent medications (to avoid any potential drug interactions), and side effect profile. Depression is one of the most costly disorders in the United States, and diagnosis is the first step in treatment. Education of the public as well as healthcare providers is the key to the treatment of depression. Once diagnosed, SSRIs can be used effectively to treat depression.



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Diagnosis and Therapeutic Management of Depression: An Update in the Use of Selective Serotonin Reuptake Inhibitors (SSRIs)

Introduction

Major depression is a common disorder in the United States. Depression is associated with high rates of relapse, long duration, and high rates of recurrence. Although effective treatment has been available for more than 35 years, it often goes underdiagnosed, misdiagnosed, or undertreated.¹ The lifetime prevalence of depression is approximately 15% of men and 24% of women. The average age of onset of depression is between ages 20 to 40 years, but occurs in up to 15% of people aged 65 years of age and older and can start during childhood or adolescence.² It is often found that many people who have depression do not seek medical help. These patients represent a significant number of people underdiagnosed in the United States.¹ Major depression is a common disorder treated in the primary care setting. Although depression is accurately diagnosed in the primary care setting, adequate treatment for depression is not given. Patients often go underdosed or treatment is not given for an adequate period of time.³ One of the most devastating complications of depression is suicide. Approximately 15% of patients with untreated or inadequately treated depression will commit suicide.^{2,4} For this reason, it is important to recognize, diagnose, and treat depression with the agents available in the United States.

Because of the reasons stated above, depression can be a major economic burden on society. If depression is not diagnosed and treated it can impact on many aspects of family, society, and the workplace. The costs of depression can be divided into 2 categories—direct and indirect. The direct costs include inpatient and outpatient care as well as cost of medications. Indirect costs include absenteeism and decreased productivity in the workplace and premature death (from suicide), which leads to a reduction in lifetime earnings.¹ A study by Greenberg et al⁵ lists an estimate of the total economic burden of depression in 1990 at \$43.7 billion. The direct costs were estimated to be \$12.4 billion, mortality costs at \$7.5 billion, and morbidity costs at \$23.8 billion. The authors list these estimates as conservative. As depression is an underdiagnosed illness, the total costs would be increased if all patients were identified and treated. Another reason for the conservative estimate is the inability to quantify the decline in the quality of life that is experienced by people with depression. All of these factors must be taken into account when looking at the economic impact of depression on society.

Recognition and Diagnosis of Depression

Health care providers can help to decrease the economic impact on society by increasing their awareness of depression and its symptoms. The Agency for Healthcare Research and Quality (AHRQ, formerly known as The Agency for Health Care Policy and Research-AHCPR) provides primary care providers with practice guidelines. The American Psychiatric Association published the criteria for diagnosis of depression in 1994 in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (*DSM-IV*).¹ The *DSM-IV* is the most important reference for use in the diagnosis of depression. There are a number of psychiatric rating scales available to aid the clinician in diagnosis of depression. Unfortunately, there are many different scales available, and each clinician has his preference for the most effective tool. The purpose of a rating scale is to give the clinician an objective view of the patient's symptoms. Some of the available scales are the Hamilton Psychiatric Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Beck-Depressive Inventory, and the Clinical Global Impression (CGI) Scale.⁶

When a patient presents with signs and symptoms of depression, the first thing a clinician should do is investigate other causes. Certain medical conditions such as hyper- or hypothyroidism, certain infections (influenza, tuberculosis), metabolic disorders (electrolyte imbalance), and neurologic disorders (Alzheimer's disease, Parkinson's disease) can mimic the signs of depression. Also, certain medications can cause or contribute to depression, such as alcohol, propranolol, clonidine, and oral contraceptives. Therefore, all patients who present with signs and symptoms of depression should have a complete physical examination, mental status exam, and basic laboratory workup consisting of a complete metabolic panel (electrolytes, renal and liver panels), thyroid function testing, and a complete blood count with differential to identify any medical causes. A complete medication history should be performed to determine if the patient is taking any medications that may cause depression.⁷

The *DSM-IV* defines a major depressive disorder as one or more episodes of major depression. Major depression is defined by the following:⁸

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from the patient's previous functioning; at least 1 of the symptoms is either number 1 (depressed mood) or number 2 (loss of interest or pleasure) below.
1. Depressed mood most of the day or nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or others' observations (e.g., appears tearful).
 2. Markedly diminished interest or pleasure in all or almost all activities most of the day or nearly every day (as indicated either by subjective account or others' observation).
 3. Significant weight loss, when not dieting, or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day.
 4. Insomnia or hypersomnia nearly every day.
 5. Psychomotor agitation or retardation nearly every day (as observed by others, not merely subjective feelings of restlessness or being slowed down).
 6. Fatigue or loss of energy nearly every day.
 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
 8. Diminished ability to think or concentrate or indecisiveness nearly every day (as indicated either by subjective account or others' observations).
 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms do not meet criteria for a mixed episode.
- C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The symptoms are not a result of the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- E. The symptoms are not better accounted for by bereavement (i.e., occurring after the loss of a loved one); the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupations with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Once the clinician determines the symptoms of depression are not related to any other medical conditions or medications, treatment should be initiated. Clinicians should determine the risk of suicide before deciding treatment options. Patients at greatest risk for committing suicide include living alone, being widowed, aging, unemployment, a lack of a social support system, and the refusal to seek help. Clinicians should assess each patient and ask suspected patients the question, "Are you thinking about harming or

killing yourself?” If the clinician fears the patient is at risk, the patient should be referred to a mental health professional, and a family member should be contacted.⁹

Selective Serotonin Reuptake Inhibitors (SSRIs): An Overview

The discovery of the SSRIs has had a positive impact on the treatment of depression. Compared with the tricyclic antidepressants (TCAs), the SSRIs have a favorable side effect profile, are well-tolerated, and are relatively safe in overdose.¹⁰ Currently, there are 5 SSRIs available in the United States: citalopram (Celexa[®]), fluoxetine (Prozac[®]), fluvoxamine (Luvox[®]), paroxetine (Paxil[®]), and sertraline (Zoloft[®]). Citalopram, fluoxetine, paroxetine, and sertraline have received U.S. Food and Drug Administration (FDA) approval for use in major depression. Fluvoxamine is FDA-approved for use in the treatment of obsessive-compulsive disorder (OCD). Studies have shown that fluvoxamine is an effective agent for the treatment of depression, but it is not a FDA-approved indication at this time. Therefore, for completeness, this review will discuss all 5 of the agents. Table 1 lists general information regarding the 5 SSRIs.

Table 1. General Information on the SSRIs^{11,12,13,14,15}

Generic Name (Brand name)	Manufacturer	Indications	Initial Dose (mg/day)	Maximum Dose (mg/day)	Dosing Schedule	Cost/day (AWP) ¹⁶ * (\$)
Citalopram (Celexa [®])	Forest	Depression	20	60	QD	1.93
Fluoxetine (Prozac [®])	Dista/Eli Lilly	Depression, Geriatric Depression, OCD, Bulimia	10-20	80	QD	2.59
Fluvoxamine (Luvox [®])	Solvay	OCD	50	300	QD	2.31
Paroxetine (Paxil [®]) (Paxil CR [®])	SmithKline Beecham	Depression, OCD, Panic disorder (D/O), Social Phobia	10-20 25	60 50	QD	2.23 CR** (not listed in '99)
Sertraline (Zoloft [®])	Roerig-Pfizer	Depression, OCD, Panic D/O	50	200	QD	2.27

* Average Wholesale Price

** Controlled Release

Pharmacology and Pharmacokinetics

The exact mechanism of SSRIs is unknown, but they are thought to selectively inhibit the reuptake of serotonin in the brain, thereby increasing serotonin neurotransmission. SSRIs have less affinity for α_1 -adrenergic, muscarinic, or histaminergic receptors; therefore, they have fewer anticholinergic, cardiovascular, and sedative effects compared with the TCAs.^{17,18} The pharmacokinetic profile of SSRIs is fairly similar with a few exceptions. The most important difference is that fluoxetine has the longest half-life at 4 to 6 days, and can stay in the system for up to 4 to 5 weeks. Compared with the other SSRIs, the

effects of fluoxetine last longer due to its half-life. Fluoxetine also has a clinically active metabolite, norfluoxetine. Therefore, fluoxetine may be a better agent to use in patients with poor compliance, as it stays in the system longer compared with other SSRIs. As all of the SSRIs are extensively metabolized in the liver, they must be used with caution in those with liver dysfunction. The pharmacokinetic properties of the SSRIs are listed in table 2.

Table 2: Pharmacokinetics of the SSRIs¹¹⁻¹⁵

Generic Name	Elimination half-life (hours)	Time to peak concentration (hours)	Plasma Protein Binding (%)	Bioavailability (%)	Elimination
Citalopram	33	2-4	80	≥ 80	Liver
Fluoxetine	4-6 days	4-8	94	95	Liver
Fluvoxamine	15-26	2-8	77	53	Liver
Paroxetine	24-31	5-7	95	> 90	Liver
Sertraline	27	6-8	99	> 90	Liver

Drug Interactions

The SSRIs all are extensively metabolized by the liver. The SSRIs are metabolized through the cytochrome P450 enzyme system. The majority of the drug interactions that occur with the SSRIs are because of their effects on the cytochrome P450 system. All of the SSRIs inhibit the cytochrome P450 2D6 enzyme, with paroxetine being the most potent inhibitor and citalopram being the least potent inhibitor. The SSRIs also affect cytochrome P450 1A2 (CYP1A2), CYP2C19, and CYP3A3/4.¹⁹ It is important to know if concurrent medications are metabolized through the cytochrome P450 enzyme system, in order to prevent potential interactions. Table 3 summarizes the effects of SSRIs on cytochrome P450 enzymes.

Table 3: SSRIs' Effect on Cytochrome P450 Enzyme System^{18,20,21}

Enzyme	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
CYP2D6	+	+++	+	+++	+
CYP1A2	-	-	+++	-	-
CYP2C19	-	++	+++	-	-
CYP3A3/4	-	+	++	+	-

- Indicates minimal or no effect, + indicates mild effect, ++ indicates moderate effect, +++ indicates strong effect.

As shown in the table above, citalopram and sertraline appear to have the least effect on the cytochrome P450 enzyme system. From the available information it would appear that citalopram and sertraline would be safe to use with medications that affect the P450 enzyme system.

All 5 SSRIs interact with monoamine oxidase inhibitors (MAOIs) and should not be administered concurrently. A washout period is recommended if MAOIs are to be used following the discontinuation of an SSRI. A washout period of 5 weeks is recommended for fluoxetine because of its long elimination half-life. The remaining 4 SSRIs require at

least a 2-week washout period before a MAOI can be initiated.¹⁰ Table 4 compiles a list of the important drug interactions associated with SSRIs.

Table 4: SSRI Drug Interactions^{11-15,18,20}

Precipitant Drug	Object Drug	Effect
All SSRIs	TCA's	↑ Plasma concentration of TCA's.
Fluvoxamine	Non-sedating antihistamines Astemizole* and cisapride**	↑ Plasma levels, resulting in QT prolongation. Concurrent use is contraindicated.
Fluoxetine Fluvoxamine Sertraline	Benzodiazepines	↓ Hepatic clearance of benzodiazepines.
Fluvoxamine Citalopram	Beta Blockers	↑ Plasma concentration of beta blockers, potential for bradycardia.
Fluoxetine Fluvoxamine	Buspirone	↓ Effect of buspirone.
Fluoxetine Fluvoxamine Citalopram	Carbamazepine	↑ Plasma concentration of carbamazepine. Clearance of citalopram may be ↑.
Fluvoxamine Fluoxetine Sertraline	Clozapine	↑ Plasma concentration of clozapine.
Paroxetine	Digoxin	Paroxetine has ↓ Area Under the Curve (AUC) of digoxin; monitor digoxin levels during concurrent administration.
Fluoxetine Fluvoxamine	Haloperidol	↑ Plasma concentration of haloperidol.
All SSRIs	Lithium	Central nervous system (CNS) toxicity, possible serotonin syndrome, or may induce a manic episode. Monitor lithium levels if used concurrently.
Fluoxetine Sertraline	Phenytoin	↑ Plasma concentration of phenytoin.
All SSRIs	St. John's Wort	Increased sedative-hypnotic effects may occur. Possible serotonin syndrome.
Fluvoxamine Paroxetine	Sumatriptan	May cause weakness, hyperreflexia, and incoordination. Use with caution.
Fluvoxamine Paroxetine	Theophylline	↓ Clearance of theophylline. Monitor levels closely if used concurrently.
All SSRIs	Warfarin	↑ Anticoagulant effect of warfarin. Monitor PT/INR closely if used concurrently.
All SSRIs	MAOIs	Potentially fatal interaction because of serotonin excess.
Phenobarbital	Paroxetine	↓ Plasma concentration and $t_{1/2}$ of paroxetine.
Cimetidine	Paroxetine Sertraline	↑ Plasma concentration of paroxetine and sertraline.
Phenytoin	Paroxetine	↓ Plasma concentration and $t_{1/2}$ of paroxetine.
L-tryptophan	All SSRIs	↑ Serotonergic effects of SSRIs and may ↑ GI and CNS side effects.

* Astemizole no longer available in the United States.

** Cisapride is to be withdrawn from the United States market in June 2000.

Adverse Effects of SSRIs

The advantage of using the SSRIs compared with the TCAs is that SSRIs appear to have fewer systemic side effects. This has helped to change the treatment of depression. Because of their pharmacology, the SSRIs have less anticholinergic and cardiovascular side effects. The most common side effects of the SSRIs are gastrointestinal (GI), such as nausea, diarrhea, constipation, and vomiting. The SSRIs also produce CNS side effects that include headache, insomnia, somnolence, nervousness, and sexual dysfunction (males and females). Most of these side effects are mild, and tolerance develops within a month. There may be certain side effects, such as sexual dysfunction and sedation, that may not resolve with continued use of the SSRI.¹⁰ All 5 SSRIs have a similar side effect profile with a few exceptions. Fluoxetine tends to be more stimulating and would be effective for use in retarded depression. Whereas fluvoxamine and paroxetine tend to be more sedating and would be effective for use in agitated depression. All SSRIs cause sexual dysfunction, which can be upsetting to the patient. Sexual dysfunction has been reported in up to 60% of patients taking SSRIs.¹⁰ These side effects include impotence, anorgasmia, delayed ejaculation, and decreased libido. These effects may not diminish with continued SSRI use; therefore, antidepressants with less effect on sexual functioning should be substituted (i.e., bupropion or nefazodone). The clinician should be aware of the side effect profile of each of the SSRIs when determining the best agent for his/her patient. Table 5 lists the most common adverse effects and their frequency of the 5 SSRIs.

Table 5: Common Adverse Reactions of SSRIs (%)¹¹⁻¹⁵

Adverse Reactions	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Cardiovascular					
Palpitations	-	2	3	3	≥ 1
Vasodilatation	-	3	3	3	-
Orthostatic Hypotension	≥ 1	-	≥ 1	-	< 1
Chest Pain	-	1.3	-	3	≥ 1
CNS					
Insomnia	15	20	21	13	22
Headache	-	21	22	18	26
Somnolence	18	13	22	23	14
Asthenia	-	12	14	14-22	≥ 1
Nervousness	-	13	12	6-9	6
Anxiety	4	13	5	5	4
Dizziness	-	10	11	13	13
Tremor	8	10	5	8	9
Myoclonus/twitching	-	0.1-1	≥ 1	3	1
Decreased libido	2	4	2	6	6
Agitation	3	≥ 1	2	5	6
GI					
Nausea	21	23	40	26	28
Diarrhea	8	12	11	12	20
Dry Mouth	20	10	14	18	15
Anorexia	4	11	6	6	6
Constipation	-	4.5	10	14	7
Vomiting	4	3	5	-	4
GU					
Sexual dysfunction/ impotence/anorgasmia	3	2	2	6.5	≥ 1
Abnormal ejaculation	6	-	8	22	14
Urinary frequency	-	1	3	3	2
Miscellaneous					
Weight gain	≥ 1	≥ 1	≥ 1	≥ 1	≥ 1
Weight loss	≥ 1	2	≥ 1	≥ 1	≥ 1
Excessive sweating	11	8	7	12	7

Abrupt withdrawal of SSRIs following chronic treatment may result in adverse effects. It has been hypothesized that the risk of side effects upon discontinuation of SSRIs is related to the drug half-life. A study by Zajecka et al²² evaluated the effects of stopping fluoxetine abruptly. It was determined that abrupt discontinuation of fluoxetine in 395 subjects after 12 weeks of administration was well-tolerated by patients and was not associated with clinical risk. Another study by Rosenbaum et al²³ selected patients taking fluoxetine, paroxetine, or sertraline on a chronic basis for 4 to 24 months. A total of 242 patients had their SSRI therapy stopped for 5 to 8 days during treatment to determine the effects of discontinuation. The results showed that patients receiving fluoxetine had statistically fewer adverse events compared with patients on sertraline or paroxetine. The symptoms that were reported included worsened mood, irritability, agitation, dizziness, confusion, headache, and nervousness. The patients treated with sertraline and

paroxetine also experienced symptoms of depression during the discontinuation phase. These 2 studies show that the discontinuation syndrome may be associated with the half-life of the drug. It appears that fluoxetine, which has a half-life of 4 to 6 days, may be associated with fewer adverse events upon withdrawal. More studies need to be performed to determine if the effect is based solely on drug half-life. Based on the current literature, clinicians should use caution when discontinuing the SSRIs. Abrupt discontinuation can lead to unwanted side effects.

Another advantage in the use of SSRIs has been their reported safety in overdose. This is especially true if the SSRIs are the only drug ingested in an overdose.¹⁰ A review article by Barbey et al²⁴ looked at FDA case reports of the SSRIs involved in overdose. The review listed the FDA-reported overdoses associated with each SSRI since their availability in the United States. In each case report, the SSRI listed was the only agent involved in the overdose. The doses ingested in each of these cases averaged from as little as 30 times the normal adult dose to ≥ 150 times the normal dose.

- Fluoxetine has been associated with 34 fatal overdoses.
- Sertraline has been associated with 8 fatal overdoses.
- Paroxetine has been associated with 6 fatal overdoses.
- Fluvoxamine has been associated with 1 fatal overdose.

At the time the article was written, citalopram was not available in the United States; therefore, there were no FDA reports of overdose related to citalopram. The authors concluded that although there is a potential for overdose with the SSRIs, they are safer in overdose compared to the TCAs. Approximately 100 to 150 fatal overdoses due to TCA ingestion are reported yearly to the American Association of Poison Control Centers, whereas only 16 fatal overdoses due to SSRIs were reported from 1987 through 1996.²³ The SSRI-related fatalities listed in this review occurred at very large doses, as listed above. Therefore, compared with the TCAs, the SSRIs appear less lethal in overdose situations.

Comparison of Clinical Trials

There are many studies published that compare the SSRIs to placebo and/or to TCAs. However, the purpose of this review is to determine whether or not any of the SSRIs is more efficacious compared with one another. Therefore, the only studies included in this review are head-to-head comparisons of SSRIs. Compared with the amount of studies available that compare SSRIs with TCAs, very few articles have been published that compare individual SSRIs.

Fluoxetine vs. Paroxetine

De Wilde et al²⁵ performed a double blind, randomized, parallel study lasting 6 weeks that compared the efficacy and tolerability of paroxetine and fluoxetine in depressed patients. Patients were assessed using the HAM-D scale. A total of 78 patients completed the 6-week study, 37 paroxetine patients and 41 fluoxetine patients. There were no differences between treatment groups with respect to demographic characteristics. The dosage range of paroxetine patients was 30 to 40 mg per day,

whereas the dosage range for fluoxetine patients was 40 to 60 mg per day. The change from baseline in the mean HAM-D total score showed no difference between the treatment groups at weeks 1, 3, 4, or 6. Both groups showed a reduction from baseline in the HAM-D scores, which relates to improvement in symptoms of depression. The only difference in treatment occurred at week 3. The paroxetine group had a statistically significant improvement ($P < .05$) in HAM-D scores compared with the fluoxetine group. This may mean that paroxetine has a faster onset of action compared with fluoxetine. With regard to adverse effects, there were no statistically significant differences between the two treatment groups. The most common side effects reported were nausea and vomiting, which were reported by 10 patients in each group. The adverse events reported in the study mirrored the events reported by the manufacturers. Overall, fluoxetine and paroxetine have similar efficacy in the treatment of depression. Paroxetine may have a faster onset of action (3 weeks) compared with fluoxetine, but at 6 weeks, both agents showed similar improvements in HAM-D scores. Both agents had comparable side effect profiles, with the most common side effects being nausea and vomiting.

Maurizio²⁶ et al performed a 12-week, multicenter, placebo-controlled, randomized, double-blind comparison of the efficacy and tolerability of paroxetine and fluoxetine in patients with major depression. The dose of paroxetine ranged from 20 to 50 mg per day and the dose of fluoxetine ranged from 20 to 80 mg per day. A total of 128 patients participated in the study, 55 patients in the paroxetine group, 54 patients in the fluoxetine group, and 19 patients in the placebo group. The efficacy tool for depression used in this study was the HAM-D scale. There were no significant demographic differences between treatment groups. Of the 128 patients, 36 did not complete the study, 15 of which dropped out because of adverse events (9 paroxetine and 6 fluoxetine). An equal number of patients in each treatment group dropped out of the study. Therefore, a total of 92 patients completed the study, 39 in the paroxetine group, 38 in the fluoxetine group, and 15 patients in the placebo group. The HAM-D scores were decreased for all treatment groups at the end of 12 weeks compared with baseline levels. No differences were seen between the treatment groups including the placebo group. The response rates (58% for paroxetine, 57% for fluoxetine, and 53% for placebo) were not significantly different at the end of the study period. The most common adverse events reported in this study were gastrointestinal, anticholinergic, sedation, and nervousness/agitation. There were no significant differences in the incidence of adverse events. The study showed that paroxetine, fluoxetine, and placebo were equally effective in treating depression. This is an interesting assumption for the authors to make considering no difference was shown between placebo and active drug. The authors cite the small placebo group ($n = 15$) as a reason for the results. It was thought that either the entire sample size was too small to show a difference or that the patient population had a mild to moderate level of depression; therefore, a difference was not seen in the results. Despite the placebo results, the study showed that paroxetine and fluoxetine are equally efficacious and well-tolerated in the treatment of depression.

Chouinard²⁷ et al conducted a 12-week, randomized, double-blind comparison of paroxetine and fluoxetine in patients with depression. Patients received either 20 to 50 mg of paroxetine per day or 20 to 80 mg of fluoxetine per day. Treatment response was

assessed using the HAM-D and CGI scales. 203 patients were enrolled in the study. A total of 130 patients completed the study, 62 patients in the paroxetine group and 68 patients in the fluoxetine group. The number of patients who did not complete the study was similar between the 2 treatment groups. The HAM-D scores decreased in both treatment groups over the 12-week study period. Treatment response was reported at 85.7% in the paroxetine group and 88.4% in the fluoxetine group. These results were not statistically different. The CGI scores also decreased in the both treatment groups with paroxetine showing a greater response at week 2 compared with fluoxetine ($P = .05$). There were no other differences in CGI scores shown during the 12-week period. The most common adverse events reported in the study were nausea, headache, and insomnia. The incidence of adverse events was not statistically significant. This study proved that paroxetine and fluoxetine were equally effective in the treatment of depression. Both agents had similar side effect profiles and were generally well-tolerated.

Citalopram vs. Fluoxetine

Patris et al²⁸ performed a multicenter, double-blind, fixed-dose, randomized trial over an 8-week period that compared citalopram to fluoxetine in the treatment of unipolar depression. Patients were assessed with the following tools: the Montgomery-Asberg Depression Rating Scale (MADRS), the HAM-D, and the Investigator's CGI. The patients received either 20 mg of fluoxetine or 20 mg of citalopram. Of the 357 patients enrolled in the study, a total of 45 patients withdrew prior to completion. A total of 312 patients, 149 in the citalopram group and 163 patients in the fluoxetine group, completed the study. There were no significant demographic differences between treatment groups. At the end of 8 weeks, the results showed improvements in the MADRS, HAM-D, and CGI scores compared with baseline in both treatment groups. None of the differences between treatment groups was statistically significant. The only statistically significant difference in response was seen after 2 weeks of treatment. A statistically significant decrease in MADRS score in the citalopram group ($P = .048$) was seen compared with the fluoxetine group. A significant reduction ($P = .025$) was also seen in the HAM-D score in the citalopram group after 2 weeks compared with fluoxetine. The CGI score showed no statistical significance at week 2 in either treatment group. In both treatment groups, the incidence of adverse events was similar. The most frequently reported side effects were nausea, insomnia, anxiety, and headache. Citalopram and fluoxetine were equally efficacious and well-tolerated in the treatment of depression after 8 weeks. The only difference in treatment groups came after 2 weeks, in which there was a significantly better response to citalopram compared with fluoxetine. This shows that citalopram may have a faster onset of action than fluoxetine, but both are equally effective in the treatment of depression.

Citalopram vs. Fluvoxamine

Haffmans et al²⁹ conducted a 6-week, double-blind, multicenter, randomized, parallel group comparison of citalopram and fluvoxamine in patients with depression. The daily doses of citalopram ranged from 20 to 40 mg, and fluvoxamine doses ranged from 100 to 200 mg during the 6 weeks of treatment. The primary efficacy tool was the HAM-D scale. A total of 217 patients were included in this study, 108 patients in the citalopram group and 109 patients in the fluvoxamine group. Twenty-one patients in the citalopram

group and 29 patients in the fluvoxamine group were withdrawn from the study as a result of adverse events. There were no significant demographic differences between treatment groups. After 6 weeks of treatment, both treatment groups showed a considerable decrease in HAM-D scores compared with baseline scores. There were no significant differences in reduction of HAM-D scores between the two treatment groups. A substantially higher rate of diarrhea was seen in the fluvoxamine group compared with the citalopram group ($P = .026$). The fluvoxamine group also experienced more nausea compared with the citalopram group ($P = .017$). The fluvoxamine group experienced a higher incidence of vomiting, but the difference was not significant. This study showed that citalopram and fluvoxamine have similar efficacy in the treatment of depression. A difference between the treatment groups was shown in the adverse effect profile. Citalopram produces fewer gastrointestinal side effects compared with fluvoxamine and appears to be better tolerated. But the overall effect on the symptoms of depression was similar.

Citalopram vs. Sertraline

Ekselius et al³⁰ performed a 24-week, double-blind, multicenter trial comparing sertraline and citalopram in patients with depression. The dose of sertraline ranged from 50 to 150 mg per day and the dose of citalopram ranged from 20 to 60 mg per day. The efficacy tools used in this study were the MADRS scale and the CGI scale. Four hundred patients were included in the study, 200 in the sertraline group and 200 in the citalopram group. During the 24-week study, 132 patients dropped out either because of adverse events or noncompliance. A total of 308 patients completed the study, 145 in the sertraline group and 163 in the citalopram group. There were no significant demographic differences between treatment groups. The MADRS scores in the sertraline and citalopram groups were significantly decreased from baseline after week 2 through the end of the study. There was no difference in response between the two treatment groups. The CGI severity scores in both treatment groups were significantly decreased compared with baseline levels. There were no differences between treatment groups. At the end of 24 weeks, 89.7% of patients in the sertraline group responded to treatment compared with 92.6% of patients in the citalopram group. The response rates were not significantly different. With regard to adverse events, the most frequent adverse events were diarrhea, increased sweating, dry mouth, and headache. There were no significant differences in adverse events between the treatment groups. Overall, the initial response rate occurred rather early (at 2 weeks) and continued throughout the 24-week period. The response rate for both the sertraline and citalopram groups was high, but the study showed no difference between treatment groups with respect to efficacy or adverse events. Therefore, sertraline and citalopram were found to be equally effective in the treatment of depression over a 24-week period.

Fluoxetine vs. Sertraline

Sechter³¹ et al conducted a 24-week, multicenter, double-blind, comparative study of sertraline and fluoxetine in patients with depression. Patients were randomized to receive either 50 to 150 mg of sertraline per day or 20 to 60 mg of fluoxetine per day. Treatment response was assessed using the HAM-D and CGI scales. Patients were also monitored from baseline to endpoint with the Leeds Sleep Evaluation scale. The Leeds scale

measures the time needed to get to sleep, difficulty getting to sleep, the amount of restfulness, and the amount of wakefulness. A total of 238 patients entered the study. There were no significant demographic differences between treatment groups. A total of 167 patients completed the 24-week study, 88 patients in the sertraline group, and 79 patients in the fluoxetine group. Sixteen patients in each group (32 total) discontinued treatment due to lack of efficacy. The HAM-D scores decreased significantly ($P < .001$) over the study period compared with baseline in both treatment groups. The sertraline group showed a greater decrease in the global scores compared with the fluoxetine group, but the differences were not significant. Individual items on the HAM-D scale were analyzed, and 3 of the items showed significant differences, with the sertraline group showing a better response. Statistical significance was seen in the sertraline group for insomnia onset ($P = .04$), agitation ($P = .02$), and general somatic symptoms ($P = .008$). The CGI scores also decreased over the study period, with sertraline showing a greater response compared with fluoxetine, but the difference was not statistically significant. At the end of the study, the CGI scores approached statistical significance in response to treatment, 47% in the fluoxetine group compared with 59% in the sertraline group ($P = .07$). With respect to the Leeds Sleep Evaluation scale, the sertraline group showed a greater improvement compared with fluoxetine, but the difference was not statistically significant. The most commonly reported side effects in both treatment groups were nausea and headache. There were no significant differences between the two treatment groups. This study showed that sertraline and fluoxetine are equally effective in the treatment of depression. Both agents were well-tolerated with few adverse events.

Discussion

A discussion of the previously mentioned clinical trials comparing the various SSRIs available in the United States is warranted. It is well known that the treatment of depression is challenging because the time to peak medication response averages from 4 to 6 weeks.¹¹⁻¹⁵ One of the major problems with the published clinical trials of antidepressants is the duration of the study. Of the 7 trials discussed in this review, 3 lasted as few as 6 to 8 weeks, and only 2 lasted as long as 24 weeks. It is difficult to evaluate an antidepressant medication if it has not reached its peak effect. The length of treatment for each study was widely varied, therefore making it difficult to directly compare the results.

Another limitation in antidepressant studies is the methodology used to assess treatment response. In the diagnosis of depression there are many different scales available to determine the degree of depression. Each clinician chooses the scale he/she feels most comfortable with or has used in the past. Because there is no standardized scale that a clinician has to use, variability arises within the trials published in the literature. This makes comparison of treatment response difficult, at best. Unlike hypertension or diabetes, where the clinician objectively treats a patient to a goal blood pressure or blood glucose level, the treatment of depression is quite subjective. Therefore, evaluation of the literature is more challenging.

Direct comparisons of the 5 SSRIs are not very common in the literature. Each of the 7 studies previously reviewed show that the SSRIs are comparable in efficacy and

tolerability with few exceptions. For example, fluoxetine was shown to have a slower onset of action in 3 of the studies, but, overall, has similar efficacy after 2 to 3 weeks of treatment. Fluvoxamine was shown in the Haffmans trial to cause more gastrointestinal side effects compared with citalopram, but was as efficacious. Overall, the studies show that the SSRIs are similar, and can be used interchangeably in the treatment of depression. Because the agents are comparable, the clinician has to choose each agent based on the patient's symptoms and potential drug interactions. Therefore, the choice of SSRI should not be based on which agent is more efficacious but on the drug interaction and side effect profile. For example, for a patient with agitated depression, the SSRI chosen should have a higher incidence of sedation. Therefore, paroxetine and fluvoxamine would be appropriate choices for the patient. Patients with hypersomnia should be given an SSRI that has a stimulating effect, such as fluoxetine. For patients needing immediate symptom response, such as suicidal patients, fluoxetine may not be the best choice because of its slower onset of response. These are just a few examples of how to choose the best agent for the patient.

Choosing the best SSRI is challenging in practice. The clinician needs to use all of the information available to make the best choice for his patient. All 5 SSRIs available in the United States are equally efficacious in the treatment of depression. When choosing an agent, the symptoms of depression, side effect profile, and potential drug interactions should be taken into account. Once an agent is chosen, the clinician or pharmacist should educate the patient about his/her illness, the side effects of the medication, and when to expect an improvement in symptoms. Patients should be frequently monitored for side effects and signs of improvement.

Improvement in Diagnosis and Treatment

Depression is a common disease in the United States. Up to 15% of depressed patients will commit suicide because of misdiagnosis or undertreatment. Some of the things we can do as health care providers to increase awareness about depression are:¹

- Educate the patient and family about depression and the available treatments.
- Develop practice guidelines and protocols for all practitioners regarding the treatment of depression.
- Provide educational programs to increase provider awareness about the diagnosis and treatment of depression.
- Increase research and development for new treatment strategies.

Pharmacists can help by counseling patients with each visit to the pharmacy. Inquire about side effects and symptom improvement and make sure that patients are getting adequate follow-up from their primary care provider or psychiatrist.

Summary

Depression is a common disease that often goes untreated. The SSRIs have made an impact in the treatment of depression because of their favorable side effect profile, tolerability, and relative safety in overdose. These agents allow clinicians to treat their patients with the fewest side effects. Although the SSRIs have helped revolutionize the

treatment of depression, education and increased awareness by healthcare providers as well as increased awareness by the public will help take the stigma out of using medications for the treatment of depression.

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