

An Overview of SSRIs for the Treatment of Depression

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Depression is a common illness which carries with it a high degree of morbidity and mortality. It is a serious disorder that interferes more with physical and mental functioning than other chronic conditions such as hypertension, arthritis, and diabetes. Major depression significantly affects the quality of life and productivity of the patient. Early recognition and treatment are essential in order to minimize the personal and societal cost associated with depression. The annual costs of depression were estimated to be \$43.7 billion in 1990. Direct costs, such as hospitalization, outpatient care, and drug treatment, account for \$12.4 billion, while indirect costs incurred by lost productivity and absenteeism (\$23.8 billion) and suicide-related losses in productivity (\$7.5 billion) comprise the remainder. Of the total cost of depression, only 2% (\$890 million) was attributed to antidepressant therapy. Thus, the majority of the costs are due to the social and occupational consequences of the disease.

In spite of the serious consequences associated with untreated depression, most studies report that it remains largely underdiagnosed and inadequately treated. Nevertheless, it is encouraging to note that if treated early and appropriately with an antidepressant, approximately 60% to 70% of patients respond to the initial course of therapy. Treating depression requires an understanding of the gravity of the illness and thorough consideration of the individual factors of each case. People respond differently to a variety of treatments, and with some knowledge of the therapeutic modalities available (both pharmacologic and non-pharmacologic treatments) coupled with a reasonable amount of patience on the part of both the health care provider and the patient, treatment can be highly successful in regaining an appropriate level of well-being.

Prevalence of Major Depressive Disorder

The National Comorbidity Survey was a nationwide study of the U.S. population conducted to estimate the prevalence and examine the risk factors of major depression. From the results of this study, the prevalence of a current (30-day period) episode of major depression was estimated to be 4.9%, while the overall prevalence of lifetime major depression was estimated to be 17.1%. Annually, approximately 10% of the population suffer from a depressive illness. The average lifetime prevalence of depression ranges from 12% for males to 26% for females. Demographic characteristics associated with a higher risk of depression include female sex, lower level of education, separated/widowed/divorced/never married status, and employment classification as homemaker or "other."

Most of the literature pertaining to the epidemiology of depression reports similar recurrence rates and risk factors. Recurrence rates in depressed individuals are high: approximately 50% of patients who initially suffer a major depressive episode will develop another. Depression is often reported to be twice as frequent in women than in men, with a high incidence among the medically ill. Genetic factors influence the development of depression as well. First-degree biological relatives are reportedly 1.5 to 3 times more likely to develop major depressive disorder than the general population. The prevalence of depression is significantly higher among elderly people in nursing homes compared to the elderly living in the community. Thus, there are a variety of factors that influence the development of a depressive disorder.

Biological Basis of Depression

The exact biological cause of depression has not been determined, however there are various theories relating to the mechanism responsible for the development of depression. The most notable theories include the biogenic amine hypothesis and the permissive hypothesis. According to the biogenic amine hypothesis, depression may be caused by inadequate transmission of monoamines, most notably norepinephrine. According to the permissive hypothesis, low serotonin levels may cause affective states, but the type of state is governed by norepinephrine levels. If there is excess norepinephrine the patient presents with mania, while a lack of norepinephrine causes depression. Other theories include the dysregulation hypothesis, which emphasizes the failure of the homeostatic regulation of the neurotransmitter systems, rather than absolute increases or decreases in their activity, and the receptor sensitivity theory, which hypothesizes that changes in sensitivity of norepinephrine or serotonin receptors may relate to the onset of depression. Also of note is the dopamine hypothesis which theorizes that depression is associated with changes in dopamine metabolism. While there is no known definite biological cause for depression, most theories relate to the change in neuroreceptor functioning.

Diagnosis of Major Depressive Disorder

A diagnosis of depression is confirmed when the patient

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Table 1**DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSION**

1. Significant weight loss or weight gain, or decrease or increase in appetite.
2. Insomnia or hypersomnia.
3. Psychomotor agitation or retardation as observed by others.
4. Fatigue or loss of energy.
5. Feelings of worthlessness, or inappropriate guilt.
6. Diminished ability to think or to concentrate.
7. Recurrent thoughts of death, suicidal ideation, suicide attempt or a specific plan for suicide.

meets established criteria which target the symptoms typically associated with depression. To meet the established criteria, a patient must exhibit either depressed mood or diminished interest or pleasure in usual activities and must have at least five symptoms from Table 1 during the same 2-week period. To facilitate the diagnosis, the patient should be asked about a family history and about previous episodes of depression.

Once a diagnosis of depression has been established, it is necessary to investigate the possibility of a medical, psychiatric, and/or drug-induced cause. Depression is often comorbid with another disease; it may occur with cancer; endocrine disorders; CNS diseases such as epilepsy, multiple sclerosis, Parkinson's disease, stroke, and Alzheimer's disease; conditions associated with loss of function or chronic pain; and chronic infections. Depression is often not diagnosed in patients with the above mentioned illnesses.

Depressive illness may be a side effect of many commonly administered drugs. Table 2 shows some drugs that have been implicated. In some cases, drugs can cause a true psychiatric depression, while others will cause such side effects as lethargy and fatigue that mimic the symptoms of depression.

Table 2: (Note: This list is not all- inclusive.)**CLASSES OF DRUGS ASSOCIATED WITH DEPRESSIVE SYMPTOMS**

Drugs of Abuse	Gastrointestinal Drugs
<i>Alcohol</i>	<i>Cimetidine</i>
<i>Amphetamines</i>	<i>Metoclopramide</i>
<i>Cocaine</i>	Cytotoxic Drugs
<i>Marijuana</i>	<i>Ifosfamide</i>
<i>Opiates</i>	<i>Uracil mustard</i>
<i>Phencyclidine</i>	Corticosteroids
<i>Sedative-hypnotics</i>	<i>Corticotropin</i>
Antihypertensive Drugs	<i>Hydrocortisone</i>
<i>Beta-blockers</i>	<i>Prednisone</i>
<i>Clonidine</i>	<i>Methylprednisolone</i>
<i>Guanethidine</i>	Oral Contraceptives
<i>Methyldopa</i>	
<i>Reserpine</i>	

Overview of Pharmacologic Management of Major Depressive Disorder

Depression is often untreated, resulting in significant societal costs. However, with the many antidepressants that are available, depression can be successfully treated. After a diagnosis of major depression has been established, the clinician must select a medication and determine the appropriate dose, taking into account both the safety and efficacy profiles. Four classes of antidepressants are available: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and atypical antidepressants. The tricyclic antidepressants and MAOIs are the first-generation and are effective and inexpensive, but have significant side effects and can be quite dangerous in overdose. The second-generation antidepressants, SSRIs and atypical antidepressants, are highly effective, better tolerated, and are safe in overdose, but are more expensive. These drugs are increasingly prescribed by psychiatrists and are considered first-line agents in the treatment of depression. Generally, even though the SSRIs cost substantially more than TCAs, and TCAs have been found to be equally effective for the treatment of depression, SSRIs are considered more cost-effective because of their tolerability and safety in overdose.

Mechanism of Action of SSRIs

The antidepressant properties of SSRIs are due to the increased concentrations of 5-HT at the synaptic cleft, enhancing serotonergic transmission and inducing the down-regulation of postsynaptic receptors. Although neurotransmitter reuptake inhibition is an important property of SSRIs, the temporal difference between the rapid onset of this effect and the slower symptomatic relief suggest that secondary adaptive responses may be contributing to the effectiveness of these agents as antidepressants.

The SSRIs provide antidepressant activity by blocking the reuptake of the neurotransmitter serotonin (5-HT) at the presynaptic terminal. At clinical doses, they have negligible effects on norepinephrine and dopamine uptake and low affinity for adrenergic, cholinergic, and histaminic receptors. This pharmacologic profile accounts for both the antidepressant action as well as the favorable side effect profile of these drugs. The SSRIs provide effective antidepressant activity without the sedating, anticholinergic, or cardiotoxic effects observed with tricyclic antidepressants; this is due to the weak binding of SSRIs to adrenergic, cholinergic, and histaminic receptors. Thus, SSRIs provide good antidepressant efficacy while avoiding the toxicities associated with older drugs.

Indications

SSRIs have been shown to be efficacious for a broad range of diseases. FDA-approved indications for SSRIs are listed in Table 3. Fluvoxamine is currently FDA-approved only for the

Table 3: FDA Approved Indications for SSRIs

Citalopram	Fluoxetine	Paroxetine	Sertraline
Major Depression	Major Depression	Major Depression	Major Depression
	Obsessive-compulsive Disorder	Obsessive-compulsive Disorder	Obsessive-compulsive Disorder
	Bulimia Nervosa	Panic Disorder	Panic Disorder
		Social Anxiety Disorder	

Table 4: Pharmacokinetics of SSRIs

	Citalopram	Fluoxetine	Paroxetine	Sertraline
Absorption F(%)	80	75-90	>90	80-95
Tmax (hrs)	4-6	6-8	3-8	4-9
Half-life	35 hrs	4-6 days 4-16 days (metabolite)	21 hrs	26 hrs
Volume of distribution (L/kg)	12	25	13	25
Protein binding	80%	>95%	>95%	>95%
Metabolites	Desmethylcitalopram	Norfluoxetine	None	Desmethylsertraline
Effect of food on absorption	None	None	None	Small increase in C _{max} and AUC
Effect of patient age	Yes	Yes	Yes	Yes

treatment of obsessive-compulsive disorder and is not discussed in this paper.

Pharmacokinetics

The pharmacokinetics of the SSRIs used for the treatment of depression are presented in Table 4. Fluoxetine has a significantly longer elimination half-life compared to citalopram, paroxetine, and sertraline. Neither paroxetine, sertraline, nor citalopram has a metabolite with significant biologic activity, but the major metabolite of fluoxetine, norfluoxetine, has the capacity to inhibit serotonin reuptake and has a half life of 4-16 days. These differences are important when switching patients to other antidepressants such as MAOIs. The long half-life of fluoxetine mandates a 5-week washout period when a patient is being switched to a MAOI compared to 2 weeks for citalopram, paroxetine, or sertraline. The half-life of all SSRIs is increased in older patients and patients with hepatic impairment. It has been suggested that lower doses of these drugs be used in these patients. The dose for paroxetine has to be adjusted for renal dysfunction as well.

There is some variability in the relationship between dose and plasma levels between the SSRIs. Plasma levels of sertraline change proportionately with changes in dose while the change in plasma levels with changes in dose for fluoxetine and paroxetine is nonlinear. The dose-plasma level relationship for citalopram is not available.

Dosing

An advantage of SSRIs over the TCAs is their ease of administration and dosing. The SSRIs are generally prescribed

once a day, usually in the morning. In addition, it has been shown that dosage titration is generally not necessary for SSRIs. Dosing for the SSRIs approved for the treatment of major depression is presented in Table 5.

Efficacy

In clinical trials, the SSRIs and TCAs have demonstrated similar efficacy. Efficacy between the SSRIs has also been well-studied and has been shown to be similar. A meta-analysis conducted by Song et al compared the efficacy of SSRIs and TCAs. A total of 53 randomized controlled trials comparing the efficacy of SSRIs with those of TCAs were included in this meta-analysis. Drop-out rates were also included as part of the analysis. Results of this analysis found that the efficacy and drop-out rates were similar for SSRIs and TCAs. The authors further suggested that SSRIs should not be considered for routine use as first-line treatment for major depression. However, this analysis did not take into account the adverse effects and comparative safety of SSRIs. When this is taken into account SSRIs would be considered as first-line agents for the treatment of major depression.

A thorough Medline search was conducted to identify the clinical trials associated with SSRIs. Due to the vast number of clinical trials published, a limited number of clinical trials were analyzed. At least one published trial comparing the SSRIs to any of the other antidepressants was included. Trials comparing SSRIs head-to-head were analyzed more thoroughly to determine whether there are differences between the SSRIs. Annotations of these clinical trials are presented below.

Table 5: Dosing of SSRIs

Medication	Usual target dose (level) mg/day, to achieve in weeks 1-3	Maximum Dose	Recommended administration schedule
Citalopram	20	60	QAM
Fluoxetine	20	40-80	QAM
Paroxetine	20-30	40-60	QAM
Sertraline	50-100	150-200	QD

A summary of all the clinical trials analyzed is presented in Table 6. Most studies comparing the SSRIs to TCAs found comparable efficacy between the agents in these two classes; however, many clinical trials found that the tolerability of the SSRIs was substantially better than the tolerability of the TCAs. These trials are presented in Table 6.

Among the major rating scales used in clinical trials to evaluate therapy in depression are Hamilton Rating Scale for Depression (HAM-D), a 21-item scale that numerically scores the severity of depression based on interview; the Clinical Global Improvement Scale (CGI), a subjective seven-point scale where the interviewer rates patients from "very much improved" to "very much worse"; Montgomery-Asberg Depression Rating Scale (MADRS), the Raskin Depression Scale (RDS), the 56-item Hopkins Symptoms checklist (HSCL), and Covi Anxiety Scale. Other scales that are less commonly used include the Brief Psychiatric Rating Scale (BPRS), the General Psychiatric Impression Global Assessment Scale (GAS), and the Beck Self-Rating Depression Scale (BPRS). Most of these scales are utilized to rate the severity of depression and rank improvement in patients treated with different therapeutic interventions. Generally, improvement is considered to be a fifty percent in scores decrease from baseline on most rating scales.

Clinical Trials

Haffmans et al compared the efficacy and tolerability of citalopram and fluvoxamine in 217 patients with major depression or bipolar disorder in a six week, double-blind, multi-center, randomized, parallel group study. Patients were allowed to take benzodiazepines, other non- psychotropic medications, and domperidone during the study. No statistically significant difference in benzodiazepine use was noted between groups; however, a significantly greater number of fluvoxamine patients were treated with the antiemetic agent domperidone ($p=0.02$). The primary efficacy variable was the 17-item HAM-D total score. Additional assessment was based on the CGI, Zung Self-rating Scale for Depression, the HAM-D factors and the HAM-D total score (50% reduction of baseline score).

Both treatment groups demonstrated a reduction in HAM-D total score from baseline. The mean total score decreased from 24.7 at baseline to 16.6 at week 6 in the citalopram group

and from 24.5 at baseline to 18.0 at week 6 in the fluvoxamine group. There were no significant differences observed between the two treatment groups. Similar proportions of patients reported a 50% or greater reduction in mean total HAM-D score with 33 of 109 reporting response in the citalopram group and 31 of 109 in the fluvoxamine group. The CGI and Zung results demonstrated similar results. At baseline a majority of patients scored a CGI of three or four (moderately ill). After 6 weeks of treatment 37 patients in the citalopram group and 35 in the fluvoxamine group had a score 1 (no illness/mild illness). Significantly more fluvoxamine patients experienced nausea (+16%; $p=0.017$) and diarrhea (+13.6%; $p=0.026$). The relatively low response rate in this study may be attributed to the presence of confounding variables resulting from selection (e.g. bipolar or refractory patients), and/or issues related to study design. This study indicated that citalopram is equally efficacious to fluvoxamine and is better-tolerated.

Patris et al compared the efficacy and tolerability of citalopram to fluoxetine in 397 patients with major depression treated in general practice in a double-blind, multi-center, fixed-dose, parallel-group study. Patients received either citalopram 20 mg or fluoxetine 20 mg for 8 weeks following a one-week run-in period. The primary measure of efficacy was the change in the mean total MADRS score from baseline to end-point. A difference of at least four points in the mean change of MADRS total score was deemed clinically relevant. Additional assessment was based on the HAM-D scale and CGI ratings.

Both treatment groups had a steady decrease in MADRS mean total score from baseline. The mean total MADRS score decreased 20.7 points in the citalopram group and 19.3 points in the fluoxetine group. The difference in the score decrease between groups was neither statistically nor clinically significant. After 2-weeks of therapy, a statistically significant difference in the number of citalopram-treated patients reporting a decrease by a minimum of 50% in the total MADRS score compared with baseline was observed (53 vs 39; $p=0.048$). Significantly more patients receiving citalopram experienced a full response at the two-week point (41 vs. 25; $p=0.034$). Similar changes were observed in the HAM-D mean total score in both groups. A statistically significant difference in the HAM-D mean total score was noted between treatment groups in favor of citalopram after 2-weeks of treatment

($p=0.025$). Side effects observed were minimal and few differences were observed between treatment groups. The most frequently recorded side effects included nausea, insomnia, anxiety, and headache. Back pain occurred more frequently in the citalopram arm compared to fluoxetine ($p=0.03$), while dry mouth and weight loss were more frequently reported with fluoxetine ($p=0.06$ and $p=0.07$). This study indicated that the efficacy and tolerability of citalopram was comparable to that of fluoxetine and the onset of citalopram appeared more rapidly with evaluations favoring citalopram at week 2 observations.

Ekselius et al evaluated the efficacy and tolerability of citalopram compared to sertraline in 400 patients with major depression in a multi-center, randomized, double-blind, parallel-group study. Patients received either sertraline 50 mg or citalopram 20 mg for 24 weeks following a one-week drug-free washout period. Dosages could be increased if significant clinical improvement was not observed after four weeks. Mean doses at week 12 were sertraline 83.5 mg per day and citalopram 33 mg per day. Primary efficacy measurements included reduction from baseline in MADRS scores and CGI-severity scores at weeks 12 and 24 and the percentage of patients responding to treatment (defined as at least 50% reduction in MADRS scores in weeks 12 and 24 compared with baseline).

Both treatment groups demonstrated significant improvement over baseline in MADRS and CGI-severity scores. The mean baseline MADRS score of 28.3 decreased to 8.5 in the sertraline group and 11.0 in the citalopram group at 24 weeks ($p<0.05$). The mean CGI-severity score of the sertraline group decreased from 4.2 ± 0.8 at baseline to 1.8 ± 1.4 at week 24 while the citalopram group score decreased from 4.2 ± 0.8 at baseline to 1.6 ± 1.2 at week 24. A similar response rate was noted in both groups with 69.5% of sertraline-treated patients and 68% of citalopram-treated patients responding at week 12, and 75.5% of sertraline-treated patients and 81% of citalopram-treated patients at week 24. The most common side effects observed in both groups included sexual dysfunction, nausea, diarrhea, increased sweating, dry mouth, and headache. This study indicated that the efficacy and tolerability of citalopram was comparable to that of sertraline.

Schone et al compared the efficacy and tolerability of paroxetine and fluoxetine in 106 depressed geriatric patients in this double-masked, parallel group, 6-week trial. Paroxetine dosing was initiated at 20 mg and was increased to 40 mg as clinically indicated. Initial fluoxetine dose was 20 mg and was increased to 60 mg maximally as clinically indicated. Efficacy was assessed using the HAM-D scale. Cognitive assessment was performed using the MMSE and the SCAG.

Paroxetine and fluoxetine treatments demonstrated efficacy by the change in HAM-D score from baseline. A significant difference in favor of paroxetine was noted at week 3

($p=0.03$). Mean total MADRS scores decreased from baseline throughout treatment, with no significant differences between treatment groups at any time during the trial, based on intent-to-treat analysis. Overall, cognitive function was improved in both the paroxetine and fluoxetine treatment groups. The mean MMSE was also significantly improved at week 3 in the paroxetine treatment versus the fluoxetine group ($p=0.02$). Both paroxetine and fluoxetine were well-tolerated with no significant differences in overall incidence of adverse events between the treatment groups. Adverse events including the digestive system and the nervous system were reported most frequently in both groups.

Tignol conducted a 6-week, randomized, double-blind, multicenter comparing paroxetine and fluoxetine in depressed patients in 178 inpatients. Patients were randomized to receive either 20 mg of paroxetine or 20 mg of fluoxetine after a 3- to 7-day washout period. Patients were given a placebo between screening and baseline visit. Patients who showed an improvement of 20% in MADRS score during this time period were considered placebo responders and were excluded from the study. Patients were allowed to take chloral hydrate (500mg) for sleep. The primary efficacy measures were 14-item HAM-A score, 14-item HAM-D score, 10-item MADRS, 14-item HAD, and the CGI severity of illness score. A similar antidepressant response was obtained at 6 weeks for both fluoxetine and paroxetine on all efficacy measures. Visual Analog Scale (VAS) for anxiety was used as a secondary measure of efficacy. Results from the VAS score favored paroxetine, however this was not statistically significant. Adverse effects were similar in both groups. Nervous and gastrointestinal symptoms were most common in both groups. Weight loss was the only adverse event that occurred significantly more in the fluoxetine group compared to the paroxetine group ($p=0.05$). Based on these results, paroxetine and fluoxetine are thought to be similarly effective agents for the treatment of depression.

DeWilde et al compared the efficacy and tolerability of paroxetine and fluoxetine in 78 patients with DSM-III major depression in this randomized, parallel-group, double-masked, 6-week study. Dosing was initiated at 20 mg fluoxetine or 20 mg paroxetine and increased as clinically indicated to a maximum of 60 mg or 40 mg, respectively. Efficacy was assessed using the HRSD total score, the MADRS, the HSCL-58 and the CGI score.

The mean HRSD score showed no significant difference between treatment groups in reduction from baseline scores. At week 3, the number of responders, defined by a greater than 50% reduction in HRSD score from baseline, was 36% in the paroxetine group and 16% in the fluoxetine group. This early response in the paroxetine treatment was similarly noted by significant difference in responders, defined by greater than 50% reduction in MADRS total score ($p=0.05$), or a HRSD score of less than or equal to 14. At week 4, 53% of patients in

the paroxetine group and 23% of patients in the fluoxetine group showed a positive response on the CGI score (defined as a score of 2 or less); this difference was significant in favor of paroxetine ($p<0.01$). No significant differences were observed otherwise throughout the trial or at endpoint evaluation. Self-rated HSCL mean changes from baseline showed a significant early response at Week 1 in the fluoxetine treatment group. This response was significantly greater in the fluoxetine group for mean change in total score from baseline ($p<0.01$) and in dimensional scores for somatization ($p<0.05$), interpersonal sensitivity ($p=0.01$) and anxiety ($p<0.001$). Following week 3, the paroxetine group had larger reductions from baseline for each of the dimensional scores, although none were significant.

Data suggests that up to 50% of patients using SSRIs to treat depression will not be responsive or will be unable to tolerate these drugs. This issue of treatment failure was addressed in another trial by Thase et al. Thase and his colleagues administered fluoxetine (20-60 mg/d) to DSM-III-R patients who failed initial treatment with sertraline. The 6-week, standardized, open-label trial had 106 adult outpatient participants with a history of intolerance ($n=34$) or lack of response ($n=72$) to sertraline therapy. Primary outcome measures of success included the mean HAM-D total score changes and self-reported BDI scores. Secondary outcome measures were HAM-D factors and CGI-S scale.

The trial was completed by 91 (85.8%) of the participants. Mean HAM-D total scores decreased steadily at all assessment points during the trial. Compared to baseline, the scores were significantly better by week 2 ($p<0.05$). Starting at a baseline of 26.11, the Beck Depression Inventory scores decreased by 13.66 points during the study. These results are statistically and clinically significant ($p<0.001$). A statistically significant improvement occurred in the secondary outcome measures. Fluoxetine decreased HAM-D factors (-3.59 from baseline; $p<0.001$) and CGI-S score (-2.03; $p<0.001$). Response criteria based on HAM-D end score was met by 63.2% of subjects; 76.4% met CGI response criteria and 71.7% met the criteria for PGI response. These results suggest that SSRIs are not interchangeable and patients who fail initial treatment with one SSRI may successfully respond to treatment with a different SSRI.

Bennie et al conducted a 6-week randomized, double-masked, parallel-group trial to evaluate the efficacy of sertraline and fluoxetine in 286 psychiatric outpatients with DSM-III-R major depression or bipolar disorder. Following a washout period of up to 2 weeks, subjects were randomized to receive either fluoxetine 20 mg once daily or sertraline 50 mg once daily. Doses were increased to a maximum allowable fluoxetine 40 mg and 100 mg sertraline after 2 weeks of treatment. Primary efficacy measures consisted of the HAM-D, CGI-I and CGI-S scales. Secondary outcome measures were Hamilton

Rating Scale for Anxiety (HAM-A), Raskin Depression Scale, the Covi Anxiety Scale and the Leeds Sleep Questionnaire. Efficacy assessments were conducted at baseline and at the end of weeks 1, 2, 4, and 6.

No statistical differences existed between sertraline and fluoxetine HAM-D total score at weeks 1, 2, 4, or 6. Based on a 50% or greater decrease in HAM-D total score from baseline, 59% of sertraline-treated subjects and 51% of fluoxetine-treated patients were responders. Similar to HAM-D scores, CGI-S total scores were not significantly different between the treatment groups at any time point. The HAM-D and CGI-S scores were statistically higher than baseline for sertraline and fluoxetine at all evaluation points ($p<0.001$). By the end of week 6, 69% of sertraline-treated and 67% of fluoxetine-treated participants were responders according to CGI-I criteria (score of 1 or 2). Depressed mood and suicide item scores were significantly reduced ($p<0.001$) in both treatment groups by week 1 according to HAM-D results. No statistically significant differences existed between the groups on any HAM-D measures. The HAM-A, Raskin Depression Scale and Covi Anxiety Scale results all showed significant ($p<0.001$) improvement by week six in both treatment groups. There were no significant differences between sertraline and fluoxetine in these measures or Leeds Sleep Questionnaire results.

Safety and Tolerability

SSRIs are associated with a variety of adverse effects, which tend to be milder than the adverse effects associated with TCAs, which explains the higher compliance rates documented with SSRIs. The most common adverse effect associated with SSRIs is nausea. Vomiting has been reported but is rare in this drug class. Nausea occurs in approximately 25% of the patients on SSRIs. However, this adverse effect is mild, transient and usually dose related. Dose reduction and/or taking the medication with meals for the first few weeks is often helpful. Diarrhea associated with SSRIs is generally mild and transient. Gastrointestinal affects are more commonly associated with sertraline than other SSRIs.

SSRIs have also been associated with increased anxiety, agitation, and insomnia in a small percentage of patients.⁵¹ Paroxetine may be associated with daytime somnolence in approximately 20% of the patients, while fluoxetine is more likely to cause agitation and insomnia. Other side effects that are common with paroxetine include headache, dry mouth, insomnia, asthenia, sweating, constipation and tremor. Fluoxetine therapy may also cause headache, sedation, dry mouth, tremor, dizziness, fatigue, vision disturbances, and anorexia. Common side effects associated with sertraline therapy include headache, sedation, insomnia, tremor, dizziness, and fatigue. Citalopram is a newer agent and adverse effect reports are currently being monitored as part of post-marketing surveillance. To date, the most common adverse

Table 6: Comparative trials of SSRIs versus placebo for the treatment of depression

Study	Study Design	N	Drug and dose	Outcome variables	Results	Comments
Claghorn	R,DB,PC	71	P 10-50mg	HAM-D, MADRS, CGI, RAS, CASP	>PLB	Gastrointestinal side effects were more common in the paroxetine group
Emslie et al	DM, PC, MC	96	F 20 mg	CGI-I, CDRS-R	F>PLB	AE minimal, including rash and manic symptoms
Fabre et al	DM, PC	84	F 20-60 mg	HAM-D, CHE, RDS, PGI, CAS, HSCL-58	F>PLB	AE were few, including nausea, anorexia and anxiety.
Fabre et al	6Wk, R, MC, DM	369	S 50, 100 or 200 mg/d	HAM-D, CGI-I, CGI-S, POMS	S>PLB	200 mg dose had best symptom relief.
Heiligenstein et al	DM, MC, PC	164	F 20 mg	HAM-D, MADRS, CGI-I, CGI-S, PGI	F>PLB	Significant AE included somnolence and diarrhea. et al
Keller et al	76Wk, R, DM, PG	161	S flexible dose up to 200mg/d	Time to recurrence of major depression HAM-D, MADRS, CDS, CGI-I, CGI-S	S>PLB.	
Montgomery et al	R,DB, PC	172	P 20-40mg (52 weeks)	HAM-D	P>PLB	Paroxetine was better at preventing recurrence
Montgomery et al	MC, DB	155	C 20mg or C 40 mg	MADRS, HAM-D	C>PLB	Incidence of SEs and drop-outs were similar in each of the treatment groups
Nyth et al	DB, MC	149	C 20-30 mg	HAM-D, MADRS, CGI, GBS	C>PLB	At 6 weeks 18 patients treated with C and 8 patients in placebo dropped out.
Smith et al	R,DB,PC	66	P 10-50mg (6-weeks)	HAM-D, MADRS, CGI, HSCL	P>PLB	No difference in adverse effects between paroxetine and placebo

effects associated with citalopram include nausea, dry mouth, somnolence, increased sweating, and tremor.

Weight loss with SSRI therapy is common, and more prevalent in overweight patients. The weight loss associated with SSRI therapy is usually mild (2kg) and self-limited. Withdrawal rates for patients on sertraline and fluoxetine are similar at 1-4%, while the withdrawal rate with paroxetine is approximately 3-5%. More data is needed to determine the withdrawal rate associated with citalopram. Collectively SSRIs are better-tolerated than the TCAs, and although the SSRIs are not devoid of side effects, they do not have anticholinergic effects nor do they induce weight gain. A meta-analysis conducted by Montgomery et al to determine the discontinuation rates of SSRIs due to adverse effects found that the adverse event discontinuation rate for the SSRIs was about 15% of the discontinuation rate for TCAs. Thus, SSRIs are likely to provide better compliance and long-term continuation of therapy compared to TCAs.

Sexual Dysfunction

Sexual dysfunction is a common side effect reported with all SSRIs. SSRIs have been associated with inability to ejaculate, delayed ejaculation and anorgasmia. Sexual dysfunction may result in noncompliance and impair a patient's quality of life. Several strategies have been proposed to treat SSRI-

induced sexual dysfunction including the addition of cyproheptadine or amantadine, switching to a different antidepressant like bupropion, or taking a weekend drug holiday. A weekend drug holiday has been shown to be effective with short half-life SSRIs such as paroxetine and sertraline. Sexual dysfunction is a common side effect encountered with SSRIs and needs to be treated appropriately to prevent noncompliance.

Serotonin Syndrome

Serotonin syndrome is described as a condition characterized by changes in mental status, diaphoresis, hyperreflexia, restlessness, shivering and tremor. This condition develops when combinations of an SSRI, L-tryptophan, clomipramine, or MAOIs are administered. Consequently, SSRIs should never be used proximally or concurrently with one of these agents. It has been recommended to wait at least 5 half-lives of the parent SSRI or of its active metabolite before starting MAOI therapy.

Safety in Overdose

SSRIs have been shown to be significantly safer than TCAs in the treatment of depression. Barbey and Roose conducted an analysis of prospective studies and case reports regarding the safety of SSRIs in overdose. This analysis found that overdoses with SSRIs rarely cause fatalities. Overdoses up to 30 times the usual dose were generally associated with minor

Table 7: Comparative trials of SSRI's versus other antidepressants for the treatment of depression

Study	Study Design	N	Drug and dose	Outcome variables	Results	Comments
Baldwin et al	R,DB, PG, MC	206	N 200-600mg P 20-40mg (8-weeks)	CGI, HAM-D, HAM-A, MADRS PGA	P=N	
Beasley et al	DM,MC	136	F 20-80 mg A 75-300 mg	HAM-D, CGI-I, CGI-S, RDS, CAS, PGI	F=A	Greater incidence of anticholinergic AE, orthostatic AE and weight gain with A. Nausea and insomnia reported with F.
Bennie et al ¹⁶	DB, PC, MC	286	S 50-100mg F 20-40mg (6-weeks)	HAM-D, CGI, HAM-A, RDS, CAS, LSQ	F=S>PLB	Headache and nausea in both groups
Bignamini et al	R,DB,PG,MC	309	A 75-150mg P 20-30mg (6-weeks)	HAM-D, CGI	P=A	Adverse effects were more common in the amitriptyline group
Christiansen et al	R,DB,PG	144	A 100-150mg P 20-40mg (8-weeks)	HAM-D, CGI, VAS	P=A	Adverse effects were more common in the amitriptyline group; weight gain was more significant in the amitriptyline group
Cohn et al	R, DB, PC	120	I 80-275mg P 20-50mg (6-weeks)	HAM-D, CGI, MADRS, RDS, PGE	P=I>PL	Signs of quicker onset of action of paroxetine compared to imipramine
Cohn et al	8WK, DM, MC	241	S 50-200mg/d A 50-150mg/d	HAM-D, CGI-I, CGI-S, SCL-56, RAC	S=A	More A drop-outs due to SE than S (35% vs 28%)
Costa e Silva	DM,MC	382	F 20-40mg V 75-150mg	HAM-D, MADRS, CGI-I, CGI-S	F=V	NS difference in AE profiles.
DeWilde ¹⁴	DM,MC	78	F 20-60mg P 20-40mg	HRSD, MADRS, CGI-I, HSCL-58	F=P	P had fewer AE. Nausea and vomiting reported in both groups.
Dunner et al	R,DB,PG,MC	272	D up to 200mg P 10-40mg (6-weeks)	HAM-D, MADRS, CGI, SCL	P=D	Adverse effects were more common in the doxepin group
Ekselsius et al ¹¹	DB, MC	440	S 50-150 mg C 20-60 mg	MADRS, CGI	C=S	
Fabre	R, DB, PC	120	I 65-275mg P 10-50mg (6-weeks)	HAM-D, RDS, CAS	P=I>PL	Adverse effects were more common in the imipramine group
Feighner	R,DB,PC, PG, MC	717	I 65-275mg P 20-40mg (6-weeks)	HAM-D, CGI, MADRS, CAS, PGE	P=I>PL	Adverse effects were more common in the imipramine group
Feighner et al	R, DB, PC	120	I 65-275mg P 10-50mg (6-weeks)	HAM-D, MADRS, CGI, RDS, CAS	P>I,PL	Paroxetine had a much quicker onset of action than imipramine; High drop-out rate in the imipramine group
Feighner et al	DM, two-center	119	F 20-80mg B 225-450mg	HAM-D, HAM-A, CGI-S, CGI-I	F=B	Low AE rate in F and B. NS difference between cohorts.
Gravem et al		43	C 20-60 mg A 75-225 mg	MADRS	C=A	At 6w 8-C and 9-A gave CGI-scores of 1 or 2 (not mentally ill or mild degree of dz)
Haffmans et al ⁹	DB, MC	217	C 30 mg FV 150 mg	HAM-D, CGI, ZSRS	C=FV	

Table 7: Comparative trials of SSRI's versus other antidepressants for the treatment of depression . . . CONTINUED

Study	Study Design	N	Drug and dose	Outcome variables	Results	Comments
Kavoussi et al	17WK, R, DM, PG, MC	248	S 50-200mg/d B 100-300mg/d	HAM-D, HAM-A, CGI-I, CGI-S	S=B	B less sexual impairment
Kiev et al	R,DB,MC	60	FL 50-150mg P 20-50mg (7-weeks)	HAM-D, HAM-A	P=FV	Type of adverse effects were different between both groups
Lydiard et al	8Wk, R DM, PC	473	S 50-150mg/d A 50-125mg/d	HAM-D, CGI-I, CGI-S, MADRS, QOL	S=A.	Statistically significant SE in A (71.8%) compared to S (49.2%) p<0.01
Patris et al ¹⁰	DB, MC	357	C 20 mg vs. F 20 mg	MADRS, HAM-D, CGI	C=F	
Rapaport et al	DM,MC	100	F 20-80mg FV 100-150mg	HAM-D, CGI, HAM-A, RDS, CAS, Hopkins Symptom Checklist	F=FV	AE of nausea with F was sig (p=0.03) compared to FV. Vomiting was reported more often in the F cohort.
Ravindran et al	R,DB,PG,MC	1098	CL 75-150mg P 20-40mg (12-weeks)	MADRS, CAS	P=CL	Adverse effects were more common in the clomipramine group
Reimherr et al	R DM, PG, MC	488	S 50-200mg/d A 50-150mg/d (8-weeks)	HAM-D, CGI-I, CGI-S, SCL-56, RAC	S>PLB; S=PLB	Dissimilar side effect profiles S- sexual dysfunction A- anti cholinergic and sedation
Rosenburg et al	DB, MC	472	C 10-30 mg C 20-60 mg I 50-150 mg	CGI, HAM-D	C=I	
Schone ¹²	DM,MC	106	F 20-60mg P 20-40 mg	HAM-D, MMSE, SCAG	P>F	GI and nervous system SE f or both P and F. No sig difference between groups.
Shrivastava et al	R, DB, PC	120	I 65-275mg P 20-50mg (6-weeks)	HAM-D, CGI, MADRS, RDS, PGE	P=I>PL	High drop-out rate for imipramine
Thase et al	13Wk, R, DM, MC, PC	416	S 50-200mg/d I 50-300mg/d	HAM-D, CGI-I, CGI-S, MADRS, IDS-SR, SAS, QOL	S=I	I statistically more drop-outs due to SE compared to S (p<0.001)
Thase et al	S, OL	106	S failure F 20-60mg/d (6-weeks)	HAM-D, BDI-SR, CGI-S	F>S	Design lacks R, PG, and placebo
Tignol ¹³	R, DB, MC	178	P 20mg F 20mg (6-weeks)	MADRS, CGI, HAM-A, VAMRS, HAD	P=F	Adverse effects similar in both groups
Wheatley et al	DM,MC	133	F 20-40 mg M 15-60 mg	HAM-D, CGI, VAMRS, QLESQ	M>F	Greater incidence of dry mouth and blurred vision with M. Greater incidence of headache and nausea with F

Abbreviations:

DB=double-blind, PC=placebo controlled, MC=multi-center, R=randomized, PG=parallel group, OL=open label
A=amitriptyline, B=bupropion, C=citalopram, CL=clomipramine, D=doxepin, F=fluoxetine, FV=fluvoxamine, M=mirtazapine, N=nefazodone, P=paroxetine, PLB=placebo, S=sertraline, V=venlafaxine
CAS=Covi Anxiety Scale, CGI-I=Clinical Global Impressions-Improvement Scale, CGI-S=Clinical Global Impressions-Severity of Illness Scale, GAS=Global Assessment Scale, HAD=Hospital Anxiety and Depression Scale, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, HSCL= Hopkins Symptoms checklist, LSQ=Leeds Sleep Questionnaire, MADRS=Montgomery-Asberg Depression Rating Scale, MMSE=Mini-Mental State Examination, PGA=Patient Global Assessment, POMS=Profile of Mood States, BDI=Beck Depression Inventory, QLESQ=Quality of Life Enjoyment and Satisfaction Questionnaire, RDS=Raskin Depression Scale, SCAG=Sandoz Clinical Assessment Geriatric Scale, VAMRS=Visual Analogue Mood Rating Scale,

symptoms while ingestions of doses 50 to 75 times the usual doses resulted in symptoms including drowsiness, nausea and vomiting. At higher doses the most common side effect was seizures. ECG changes and decreased consciousness were also noted. Fatalities have only been reported when doses greater than 150 times the usual dose were ingested.

Safety of SSRIs in Cardiovascular Disease

A major disadvantage with the use of TCAs for the treatment of depression is cardiovascular side effects. All TCAs have been shown to increase heart rate and delay cardiac conduction in patients with a history of heart disease. The frequency of orthostatic hypotension also increases significantly in this patient population. Several studies have observed that this may increase the risk of orthostatic falls by up to 50% in patients with heart disease.

SSRIs, on the other hand, have been shown to be fairly safe as antidepressants in patients with heart disease. An initial study was conducted in patients with stable cardiovascular disease, who were treated with fluoxetine. The average dose after 6 weeks was 50 mg per day. This study showed almost no cardiovascular effects. Pulse rate did slow slightly, but that decrease was not dose related. A second study in depressed patients with heart disease compared paroxetine and nortriptyline. This study found that compared with nortriptyline, paroxetine was associated with a lower incidence of adverse cardiovascular effects. Overall, SSRIs have shown no signs of producing orthostatic hypotension, as seen with TCAs, or malignant arrhythmias. SSRIs have caused conduction changes in a small number of very severe overdoses.

Discontinuation Syndrome

Discontinuation syndrome occurs in one-third of the patients who stop SSRI therapy. Discontinuation symptoms can also occur when doses are frequently missed and sometimes during dosage reduction. Discontinuation syndrome consists of adverse effects that generally emerge 24 to 72 hours after the discontinuation of SSRIs and can last from 7 to 14 days. These symptoms can be distressing and may include ataxia, dizziness, vertigo, shock-like sensations, numbness, and aggressive and impulsive behaviors. Discontinuation syndrome is much more common with shorter half-life SSRIs such as paroxetine, sertraline, and citalopram than with fluoxetine. It is important to counsel the patient about discontinuation syndrome associated with noncompliance. Often, reassurance is the only treatment needed as the symptoms associated with discontinuation are short-lived. However, when the symptoms are more severe antidepressant therapy may need to be reinstated and a gradual taper may be needed. Fluoxetine generally does not need to be tapered. It has been recommended that paroxetine be tapered at a rate of 10 mg every 5 to 7 days while sertraline be tapered at a rate of 50 mg every 5-7 days. This information is not yet available for citalopram.

Drug Interactions

All SSRIs interact with the cytochrome P450 (CYP) isoenzymes at some level. Some SSRIs are more potent at inhibiting the CYP isoenzymes than others. Clinically relevant interactions are more likely to occur with fluoxetine and paroxetine compared to citalopram and sertraline. The inhibitory effect of SSRIs is concentration-dependent and is likely to be more potent at higher doses. In general, the pharmacokinetic interactions are more important for substrates with narrow therapeutic indices such as TCAs, anticonvulsants, warfarin and astemizole. A list of significant drug interactions is presented in Table 5. This list is not all-inclusive.

Fluoxetine and paroxetine are potent inhibitors of CYP2D6 even at therapeutic doses, so compounds metabolized by this enzyme such as TCAs, clozapine, risperidone, metoprolol, propranolol, and encainide should be used cautiously. Medications such as terfenadine, astemizole, cisapride, clozapine, carbamazepine and alprazolam are metabolized by the CYP3A4, which is moderately inhibited by fluoxetine. These combinations should be avoided or the substrate should be prescribed at a lower dose. Fluoxetine is also a moderate inhibitor of CYP2C19, which metabolizes diazepam and phenytoin. Thus, these medications should be monitored closely when used concurrently with fluoxetine.

Sertraline and citalopram are weak inhibitors of the CYP isoenzymes and are likely to cause fewer clinically significant interactions. Both citalopram and sertraline, therefore, have significant advantages over the current SSRIs for patients receiving concurrent drugs metabolized by the CYP isoenzymes.

Practice Guidelines

Treatment guidelines are designed to decrease the variance and increase the appropriateness of treatment, thus enhancing patient outcomes. Treatment guidelines are generally developed based on a combination of meta-analysis of randomized clinical trials and by developing a consensus recommendations by experts. The Agency of Health Care Policy and Research (AHCPR) and the American Psychiatric Association have current guidelines available for the treatment of depression. However, these guidelines were last updated in 1993 and 1994, respectively. There have been significant advances since then in antidepressant therapy which are not taken into account in these guidelines. The Texas Medication Algorithm Project (TMAP) was developed to update these guidelines. The goal of TMAP was to develop evidence-based treatment guidelines through a consensus panel. No opinion was rendered by the panel in areas where consensus was not reached. The consensus panel also decided that these guidelines should also incorporate pharmacoeconomic data when available; however, a restrictive formulary approach in the development of these

Table 8: Common drug interactions with SSRIs

SSRI	Interacting Drug	Result
Citalopram, Fluoxetine, Paroxetine, Sertraline	Monoamine Oxidase Inhibitors	May precipitate serotonin syndrome
Fluoxetine, Paroxetine, Sertraline	Desipramine	↑ plasma concentration of desipramine
Fluoxetine, Paroxetine, Citalopram	Imipramine, Amitriptyline amitriptyline	↑ plasma concentration of imipramine and
Fluoxetine	Phenytoin	↑ plasma concentration of phenytoin
Fluoxetine	Carbamazepine	↑ plasma concentration of carbamazepine (some studies have not found this interaction)
Fluoxetine, Paroxetine	Warfarin	Small studies and case reports have found a potential for ↑ PT/INR or bleeding
Paroxetine, Sertraline	Cimetidine	↑ plasma concentration of the SSRI
Fluoxetine	Lithium	Both ↑ ↓ concentrations of lithium have been reported with case reports of adverse neurologic effects. Lithium is used to augment response in treatment-resistant depression
Fluoxetine	Propranolol, Metoprolol	Case reports of heart block, tachycardia
Citalopram, Fluoxetine, Sertraline	Selegiline	Case reports of mania and hypertension with Paroxetine, fluoxetine. Selegiline manufacturer recommends against the use of SSRIs concomitantly
Fluoxetine	Alprazolam, Diazepam, Triazolam	↑ plasma concentrations of the benzodiazepine
Fluoxetine, Sertraline	Astemizole, Terfenadine astemizole and terfenadine	Cardiotoxicity due to ↑ concentrations of
Fluoxetine	Buspirone	Worsening of psychiatric condition due to the possible inhibition of the serotonergic effects of buspirone
Citalopram	Buspirone	May precipitate serotonin syndrome
Fluoxetine	Clozapine	↑ concentration of clozapine
Fluoxetine	Delaviridine	↑ trough concentrations of delaviridine
Citalopram, Fluoxetine	Sibutramine	May precipitate serotonin syndrome
Fluoxetine, Sertraline	Tramadol	Increased risk of seizures

guidelines was rejected. The treatment algorithms were developed for the treatment of major depressive disorder without psychotic features and for the treatment of major depressive disorder with psychotic features. An overview of the TMAP treatment guidelines for the management of major depressive disorder are presented below.

The treatment for major depressive disorder is divided into three phases: acute, continuation, and maintenance treatment. The goals of acute treatment are to decrease the symptoms and shorten the duration of the depressive episode. Continuation therapy begins after the acute episode has been stabilized and continues until full remission is attained. Maintenance therapy is necessary for patients who have experienced more than one depressive episode to prevent further recurrences. The TMAP algorithm is presented in Figure 1. As part of this algorithm, it is assumed that an appropriate diagnosis of depression has been made. The TMAP algorithm recommends the use of a

non-tricyclic agent as a first-line agent for the treatment of major depressive disorder. SSRIs (fluoxetine, paroxetine, or sertraline), bupropion, nefazodone, or venlafaxine are recommended as first-line agents for the treatment of major depressive disorder.

SSRIs are generally considered the first agent of choice in most patients because of supporting data about long-term efficacy, minimal necessity for dosage titration and better tolerability.

Patients who do not respond to a SSRI initially may be switched to another SSRI, an atypical antidepressant or a TCA. Patients who do not respond to these can be further managed according to the TMAP treatment algorithm. Patients who achieve remission in the acute phase should be continued on the antidepressant for at least another 6 to 9 months. According to these guidelines, tapering and discontinuation of the antidepressant should occur over a 2- to 3- month period.

Table 9: Cost of SSRIs (Prices based on 1998 Red Book)

SSRI	Available doses	Price per dose
Citalopram	20mg	\$1.93
	40mg	\$2.02
Fluoxetine	10mg	\$2.44
	20mg	\$2.50
Paroxetine	10mg	\$2.13
	20mg	\$2.27
	30mg	\$2.29
	40mg	\$2.42
Sertraline	25mg	\$2.14
	50mg	\$2.21
	100mg	\$2.28
Amitriptyline	10mg	\$0.036
	25mg	\$0.053
	100mg	\$0.95
	150mg	\$0.026
Imipramine	10mg	\$0.029
	25mg	\$0.018
	50mg	\$0.041

Patients who experience an initial episode of depression have a 50% chance of recurrence and by the third episode this increases to 90%. Thus, patients with at least one recurrent episode should be started on maintenance therapy. Patients in continuation and maintenance phase should be prescribed full therapeutic doses. Optimal duration of maintenance therapy varies from one year after continuation phase to lifetime therapy depending on the number of recurrences as well as other risk factors. For more detailed information on this algorithm, refer to reference 65.

A summary report was recently released by the AHCPR comparing the newer antidepressant drugs and herbal therapies to older antidepressants. A thorough search of the literature identified relevant clinical trials for evaluation of newer antidepressants. This report stated that there is similar efficacy between the older and newer antidepressants. However, there is a lack of data regarding treatment with more than one antidepressant, combination treatment of antidepressants with psychotherapy, and augmentation strategies with pindolol and lithium. This report also revealed that there was a need for more long-term studies with the newer antidepressants. Overall, this report states that both newer and older antidepressants should be considered in making treatment decisions. Cost and difference in drop-out rates due to adverse effects, which was slightly higher for the TCA group in this report, should also be taken into account when making treatment decisions. For a map of the Depression Algorithms, see web site mhmr.state.tx.us/meds/mddnp3.htm.

Costs and Cost Effectiveness

The overall prescribing of antidepressants has gone up annually since the early 1990s with prescribing of SSRIs

outpacing TCAs. Thus, a major issue with SSRI therapy remains the cost, which can be 10 to 15 times that of the TCAs. SSRI cost are presented in Table 8. TCAs have been shown to provide the same efficacy in clinical trials as SSRIs. Meta-analysis of dropout rates show that the differences in overall dropouts between the two therapies is not significant. Thus, arguments have been made to consider TCAs as first-line agents for the treatment of depression.

An economic evaluation of the SSRIs was conducted by the Canadian Coordinating Office for Health Technology Assessment to determine the cost-effectiveness of SSRIs. This evaluation was based on a meta-analysis of randomized controlled trials which extended over 4 to 12 week periods. This evaluation found that there was no significant difference in efficacy and overall drop-outs between the SSRI and TCA group. This evaluation found that the SSRIs were more cost-effective from a societal perspective when the health-related quality of life was taken into account.

A prospective study was conducted to determine the difference in costs comparing fluoxetine to desipramine or imipramine as initial treatment in a health maintenance organization (HMO). After 6-months of therapy, there was no difference in patient outcomes between the two groups. However, the TCA treated patients reported a higher rate of adverse effects and accounted for a higher dropout rate. Overall, the total treatment costs were similar for both groups despite the higher acquisition costs of fluoxetine.

Another study compared the direct health care costs for 701 patients prescribed either fluoxetine or one of three TCAs (amitriptyline, nortriptyline, or desipramine). This study only included patients who had remained on the same antidepressant for a period of one year. This criteria created a bias for the group likely to encounter a higher drop out rate. By removing these patients from the analysis, the average cost of therapy for each group is reduced. Health care costs and outcomes were analyzed using multivariate analysis. This analysis showed that the cost of pharmacotherapy was substantially higher for patients receiving fluoxetine; however, the savings resulting from use of TCAs were outweighed by increased spending and greater utilization of other health care services by patients in this group.

Sciar et al conducted a study to evaluate the difference in health care costs between fluoxetine, paroxetine and sertraline. A total of 744 subjects were found to satisfy the study criteria, with approximately 50% in the fluoxetine group. A multivariate analysis was conducted to evaluate the data. The authors concluded that treatment with either paroxetine or sertraline resulted in greater health care costs than treatment with fluoxetine. A major problem with this study was that the baseline severity of depression was not taken into account. The prevailing pattern of clinical practice was that fluoxetine was

used as first-line therapy while sertraline and fluoxetine were used as second-line agents. Hence, patients in the sertraline/paroxetine group were likely to be more difficult and costly to treat.

Another study comparing the total health care costs associated with fluoxetine, paroxetine, or sertraline was recently published. Health care costs for patients with a diagnosis of depression and antidepressant therapy with one of these three SSRIs resulted in a total of 2342 subjects. This analysis showed that total health care costs were similar for all three agents. Although baseline severity of depression was not taken into account, the difference in results compared to Sclar et al was the greater use of sertraline and paroxetine as first-line agents for the treatment of depression. Thus, these studies lend support to the use of any of the SSRIs as first-line agents for the treatment of depression.

Conclusions

Depression remains a highly underdiagnosed disease. Even when diagnosed appropriately the treatment is often inadequate, leading to higher rates of relapse.⁴ Because of the economic costs associated with depression, it is imperative that it is diagnosed and treated appropriately. This review has shown that the SSRIs are as effective as TCAs for the treatment of depression. When just drug costs are evaluated the SSRIs are significantly more expensive than TCAs. However, when overall health care costs are taken into account SSRIs have been shown to be cost-effective for the treatment of depression compared to TCAs. Long-term efficacy for the SSRIs is not available and more data is needed in this area. Whether the cost-effectiveness of SSRIs holds up with long-term treatment remains to be seen. ■

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