

Antidepressants, Selective Serotonin Reuptake Inhibitors (SSRI) Review

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Overview

Selective serotonin reuptake inhibitors (SSRIs) are antidepressants that block the reuptake of serotonin in the brain. Compared to the older tricyclic antidepressants (TCAs), SSRIs have less of an effect on histaminic and muscarinic receptors. The improved side effect profile leads to increased compliance with the SSRIs. While there is no evidence that the SSRIs are more effective than the TCAs, this improved tolerability, as well as the lower lethality in overdose, safety in cardiovascular disease, and lower incidence of weight gain, has resulted in the SSRIs becoming first-line agents for the treatment of depressive disorders. Additionally, some of the SSRIs may be effective for anxiety, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and eating disorders.

Depressive disorders

Major depressive disorder (MDD) has a reported lifetime prevalence of approximately 16 percent.¹ The economic burden of treating depression is substantial. Patients with depression have increased loss of workdays and more physical illnesses for which they seek medical care compared to the general population.²

Premenstrual dysphoric disorder (PMDD) is a depressive disorder with symptoms that are very similar to those of MDD. The difference between PMDD and MDD is that PMDD symptoms are cyclical, subsiding with onset of menses.^{3,4,5}

Anxiety disorders

Anxiety disorders are the most common of all the mental health disorders. This category of disorders includes generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder, OCD, and PTSD. Additional disorders in this group are specific phobias and acute stress disorders.

People with GAD experience pathological anxiety, which is excessive, chronic, and typically interferes with their ability to function in normal daily activities. Generalized or "free-floating" anxiety is distinguished from phobia because it is not triggered by a specific object or situation.

In the United States, SAD is the most common anxiety disorder affecting approximately 5.3 million people per year. It is the third most common psychiatric disorder after depression and alcohol abuse. This disorder is characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur.

Panic disorder is a severe, chronic anxiety disorder characterized by recurrent episodes of panic and the development of fear or anxiety regarding the possibility of future panic attacks. Estimates for the incidence of panic disorder range between three to six million people per year with two-thirds of those affected being female. Recent epidemiologic studies suggest that up to 15 percent of the general population experience isolated panic attacks, whereas up to 3.5 percent develop full panic disorder during their lifetime.

OCD is an anxiety disorder that is characterized by recurrent, unwanted thoughts (obsessions) and/or repetitive behaviors (compulsions). This disorder affects about every two to three people out of 100, with women and men being affected equally.

PTSD is the fourth most common psychiatric condition, affecting about 5.2 million people. The symptoms of PTSD are re-experiencing the trauma, emotional numbing, avoidance, and increased arousal.^{6,7,8,9,10,11}

Pharmacology

All SSRIs exhibit antidepressant action by blocking the reuptake of serotonin into presynaptic neurons. Serotonin is a regulatory neurotransmitter with generally inhibitory effects.¹² The serotonergic cell bodies reside in an area of the brainstem called the raphe nucleus. The serotonergic projections from the raphe nucleus extend to various locations within the brain and spinal cord. This system is believed to play an important role in the modulation of a variety of psychobiological functions such as mood (projections to the frontal cortex), anxiety/panic (projections to the limbic areas), sleep (projections to the sleep centers), consumption behavior (projections to the hypothalamus), sexual activity (spinal cord projections), motor activity (projections to the basal ganglia), and gastrointestinal function (projections to the chemoreceptor trigger zone; peripheral gut receptors).^{13,14} Increasing serotonin in these extended locations mediates both the therapeutic actions and side effects of the agents.

Citalopram (Celexa[®]) is more selective for serotonin activity than fluoxetine (Prozac[®], Prozac Weekly[™], Sarafem[®]), paroxetine (Paxil[®], Paxil CR[®], Pexeva[®]), sertraline (Zoloft[®]), and fluvoxamine (Luvox[®] is no longer sold in the United States; therefore, fluvoxamine is available only as a generic product).¹⁵ Paroxetine is the next most potent and selective inhibitor of serotonin reuptake, followed by sertraline. Escitalopram (Lexapro[™]) is the S-enantiomer of racemic citalopram. With respect to serotonin reuptake inhibition, escitalopram is 100 times more potent than the R-enantiomer.¹⁶

Minute, but discrete, differences in affinities among the SSRIs for various receptors result in variances in the secondary pharmacologic properties of these agents. It is thought that these effects on other neurotransmitters may be responsible for the small differences in the adverse effect profiles of the SSRIs.¹⁷

Pharmacologic Properties¹⁸

Drug	Serotonin reuptake inhibition	Norepinephrine reuptake inhibition	Dopamine reuptake inhibition	Serotonin 5HT2C agonist	Muscarinic/cholinergic antagonist
citalopram	X				
escitalopram	X				
fluoxetine	X	X		X	
fluvoxamine	X				
paroxetine	X	X			X
sertraline	X		X		

FDA-Approved Indications - Adult

Drug	Mfr	MDD	GAD	SAD	Panic Disorder	PTSD	OCD	PMDD	Bulimia Nervosa
citalopram (Celexa)	generic	X							
escitalopram (Lexapro)	Forest	X	X						
fluoxetine (Prozac)	generic	X	X		X		X		X
fluoxetine (Sarafem)	generic							X	
fluoxetine ER (Prozac Weekly)	Lilly	X							
fluvoxamine	generic						X		
paroxetine HCl (Paxil)	generic	X	X	X	X	X	X		
paroxetine HCl controlled release (Paxil CR)	GSK	X		X	X			X	
paroxetine mesylate (Pexeva)	JDS	X	X		X		X		
sertraline (Zoloft)	generic	X		X	X	X	X	X	

FDA-Approved Indications - Pediatric

In pediatric patients, fluoxetine is the only SSRI indicated for treatment of MDD. Fluoxetine, sertraline, and fluvoxamine are indicated for treatment of OCD in this patient population. Fluoxetine is indicated for treatment of OCD for children seven years of age and older, sertraline for children six years of age and older, and fluvoxamine for children eight years of age and older.

Pharmacokinetics

The SSRIs are similar in that they are slowly, but completely, absorbed from the gut with times to peak plasma concentrations (C_{max}) of three to eight hours.¹⁹ SSRIs are also widely distributed throughout the body (i.e., large volume of distribution, V_d). There is variation among the SSRIs; however, in their level of protein binding, metabolism, half-lives, linearity of pharmacokinetics over the usual dosage range, and effect of organ impairment on elimination.²⁰

Drug	Protein Binding (%)	Active Metabolites (half-life)	Half-Life (days)	
			Normal	Cirrhosis
citalopram (Celexa) ^{21,22}	50-80	none	1.5	3.5
escitalopram (Lexapro) ^{23,24}	clinically insignificant	none	1.1-1.4	1.6
fluoxetine (Prozac/Prozac Weekly, Sarafem) ^{25,26}	≥95	norfluoxetine (7-16 days)	2-6	7
fluvoxamine ^{27,28,29}	77-80	none	0.6-1	1
paroxetine HCl (Paxil) ³⁰	>93	none	0.4-0.9	0.8-1.3
paroxetine HCl controlled-release (Paxil CR) ³¹	>93	none	0.6-0.8	0.8-1.3
paroxetine mesylate (Pexeva) ³²	>93	none	1.4	0.8-1.3
sertraline (Zoloft) ³³	98	desmethylsertraline (2-4 days)	1-1.1	2

Because SSRIs are weakly bound to α 1-acid glycoprotein, even the highly protein bound SSRIs do not significantly increase the free fraction of other highly protein bound drugs.

Citalopram (Celexa), escitalopram (Lexapro), and sertraline (Zoloft) show linear pharmacokinetics in that a change in dose leads to a proportional change in drug concentration. The effects of the other SSRIs, which have nonlinear pharmacokinetics, would be expected to increase disproportionately with higher doses.^{34,35}

All SSRIs are dependent on oxidative metabolism for elimination with the resultant metabolites being primarily excreted through the urine. There is a 100 to 150 percent increase in plasma levels of paroxetine when administered to patients with severe renal insufficiency.³⁶ Renal insufficiency does not affect the other SSRIs.^{37,38}

Paroxetine controlled-release (Paxil CR) tablets are designed to delay the start of drug release until the tablets have left the stomach.

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Studies of less than six weeks' duration were excluded since this short timeframe may be insufficient to appropriately evaluate the effects of antidepressant agents. Studies focusing specifically on the elderly population (≥ 65 years) or on inpatients were excluded because they are not applicable to the patient population under consideration. Studies that did not use the standard rating scales described below were also excluded. For studies of bulimia, single-blinded comparative studies of more than 30 patients were included.

Efficacy scales

The two most common methods of reporting the efficacy results of antidepressant clinical trials are response rates and remission rates. Response is defined as a 50 percent reduction in severity of depressive syndrome as measured by a standardized scale or a rating of much or very much improved as assessed by a global assessment method. Remission is a full resolution of the depressive syndrome such that the patient scores in the non-depressed range on a standardized scale. In clinical trials of antidepressants, the percentage of patients who remit on placebo usually ranges from 20 to 30 percent while the remission rate on active drug is generally 45 to 60 percent. In most studies, response rates are 10 to 15 percent higher than the remission rate.

For MDD, two of the most commonly used standardized rating scales are the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS).

HAM-D (Hamilton Depression Rating Scale) – This scale is used to assess the severity of MDD in patients already diagnosed with an affective disorder. It is the most widely used and accepted outcome measure for evaluating depression severity. The HAM-D is the standard depression outcome measure used in clinical trials presented to the Food and Drug Administration by pharmaceutical companies for approval of New Drug Applications. The standard HAM-D-21

contains 21 questions. The more commonly used HAM-D-17 excludes four questions relating to diurnal variation, depersonalization and derealization, paranoid symptoms, and obsessional and compulsive symptoms. The remaining 17 questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels, and weight loss.³⁹ The HAM-D-17 provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision.

MADRS (Montgomery-Asberg Depression Rating Scale) – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.⁴⁰

Other standardized scales used in the evaluation of the drugs in this class include:

CGI-I (Clinical Global Impression – Global Improvement) – This three item scale assesses the patient's improvement or worsening.⁴¹

CGI-S (Clinical Global Impression – Severity) – This three-item scale assesses the clinician's impression of the current state of the patient's illness. The rater is asked to “consider his total clinical experience with the given population.”⁴²

HAM-A (Hamilton Anxiety Rating Scale) – This is the most frequently used and accepted outcome measure for the evaluation of anxiety in clinical trials. The HAM-A consists of 14 items, each defined by a series of symptoms such as anxiety, tension, depressed mood, palpitations, breathing difficulties, sleep disturbances, restlessness, and other physical symptoms.⁴³ The HAM-A is widely used. It is included in the National Institute of Mental Health's Early Clinical Drug Evaluation Program Assessment Manual, designed to provide a standard battery of assessments for use in psychotropic drug evaluation.

Liebowitz Social Anxiety Scale (LSAS) – The LSAS is a questionnaire whose objective is to assess the range of social interaction and performance situations that individuals with social phobia may fear and/or avoid. It is also a popular measurement tool used by researchers to evaluate the efficiency of various SAD treatments, including pharmacological trials. A modified social anxiety scale exists for children and adolescents.

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) – This is a self-reporting measure designed to enable investigators to easily obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning.⁴⁴

Panic and Agoraphobia Scale (PAS) – This is the first scale for assessing the severity of panic disorder with or without agoraphobia. Compatible with both DSM-IV and ICD-10 classifications, and available in both self-related and observer-related versions, the PAS was specially developed for monitoring the efficacy of both drug and psychotherapy treatments. The PAS has excellent psychometric properties and is quick to use. The observer-rated version can be completed in five to ten minutes.⁴⁵

VAS (Visual Analog Scale) – The VAS-Total score is a patient-rated instrument that mirrors the diagnostic criteria of PMDD as identified in the DSM-IV. It includes assessments for mood, physical symptoms, and other symptoms. The VAS is one of the most frequently used measurement scales in health care research, most commonly used for the measurement of

pain.^{46,47,48} This scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli.

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) – This is a 10-item clinician-administered scale developed to assess the severity of obsessions and compulsions, independent of the number and type of obsessions or compulsions present. Obsessions and compulsions are rated according to the amount of resistance to, distress over, control over, interference from, and time spent on them. The scale yields a total severity score as well as separate obsession and compulsion subscale scores. The Y-BOCS has been the primary outcome measure in virtually all multicenter clinical trials of SSRIs for the treatment of OCD.

Major depressive disorder (MDD)

citalopram (Celexa) versus escitalopram (Lexapro)

In an eight-week double-blind trial, 491 patients with an ongoing major depressive episode were randomized to receive escitalopram (Lexapro) 10 or 20 mg/day, citalopram (Celexa) 40 mg/day, or placebo.⁴⁹ Escitalopram (Lexapro) and citalopram (Celexa) produced significant improvement at study endpoint relative to placebo on all measures of depression. The 10 mg and 20 mg doses of escitalopram (Lexapro) showed similar improvement on the MADRS. Escitalopram (Lexapro) 10 mg/day was at least as effective as citalopram (Celexa) 40 mg/day at study endpoint. The incidence of discontinuations due to adverse events for the escitalopram (Lexapro) 10 mg/day group was not different from the placebo group (4.2 versus 2.5 percent; $p=0.5$) and not different for the escitalopram (Lexapro) 20 mg/day group and the citalopram (Celexa) 40 mg/day group (10.4 versus 8.8 percent; $p=0.83$).

Moderately to severely depressed patients in primary care were randomized to receive citalopram (Celexa) 20 to 40 mg/day, escitalopram (Lexapro) 10 to 20 mg/day, or placebo for eight weeks.⁵⁰ At the conclusion of this 469-patient double-blind study, significantly more patients had responded to treatment with escitalopram (Lexapro) than with citalopram (Celexa) ($p=0.021$) or placebo ($p=0.009$), as measured by MADRS. Both active treatments were well tolerated and had a similar adverse event profile. Both citalopram (Celexa)- and escitalopram (Lexapro)-treated patients had adverse event withdrawal rates of three to four percent which was similar to placebo.

A double-blind, randomized clinical trial was performed in which general practitioners and psychiatrists compared escitalopram (Lexapro) 20 mg/day with citalopram (Celexa) 40 mg/day over eight weeks in 280 patients with MDD.⁵¹ The primary efficacy variable, change in mean MADRS, improved more with escitalopram (Lexapro) than with citalopram (Celexa) ($p<0.05$). There were more MADRS responders with escitalopram (Lexapro) (76 percent) than citalopram (Celexa) (61 percent; $p<0.01$). Adjusted remission rates were 56 and 44 percent, respectively ($p<0.05$). Tolerability was similar in both groups. Significantly more patients withdrew in the citalopram (Celexa) group (10.6 percent) than in the escitalopram (Lexapro) group (4.3 percent; $p<0.05$).

In a double-blind, 24-week study, 357 patients were randomly assigned to treatment with escitalopram (Lexapro) 10 mg/day or citalopram (Celexa) 20 mg/day.⁵² The MADRS response rate was higher in the escitalopram (Lexapro) group than in the citalopram (Celexa) group at eight weeks (63 and 55 percent, respectively; $p<0.05$), but not at 24 weeks (78 and 80 percent, respectively; $p=NS$). Both escitalopram (Lexapro) and citalopram (Celexa) were safe and well tolerated in acute and long-term treatment, and the overall adverse event profiles for the two drugs were similar. There were statistically significantly fewer withdrawals in the escitalopram (Lexapro) group than in the citalopram (Celexa) group.

escitalopram (Lexapro)

Efficacy and tolerability of escitalopram (Lexapro) to prevent relapse of MDD in older patients who had responded to acute treatment with escitalopram (Lexapro) was investigated. The study enrolled 405 patients aged 65 years and older with a primary diagnosis of MDD and a MADRS total score of 22 or more. The patients received 12-week, open-label escitalopram (Lexapro) 10 or 20 mg per day treatment.⁵³ Remitters (MADRS \leq 12) were randomized to 24-week double-blind treatment with escitalopram (Lexapro) (n=152) or placebo (n=153). The primary efficacy parameter was the time to relapse, defined as either an increase in MADRS total score to 22 or more or lack of efficacy as judged by the investigator. A clear beneficial effect of escitalopram (Lexapro) relative to placebo on time to relapse was shown. Escitalopram (Lexapro) was well tolerated during both the open-label and the double-blind treatment periods with insignificant differences between escitalopram and placebo in withdrawal rates due to adverse events.

citalopram (Celexa) versus fluoxetine (Prozac)

General practice patients with depression were randomized to eight weeks of treatment with citalopram (Celexa) or fluoxetine (Prozac), both given 20 mg once daily.⁵⁴ In the multicenter, double-blind study of 357 patients, there were significant improvements in both MADRS and HAM-D scores with no significant differences between treatments. The onset of citalopram (Celexa) appeared more rapid with assessments favoring citalopram (Celexa) at the two-week evaluation. Except for back pain, which occurred more frequently with citalopram (Celexa), there were no significant differences between treatments with regards to adverse events.

citalopram (Celexa) versus fluvoxamine

In a multicenter double-blind study, 217 patients with MDD were randomized to treatment with citalopram (Celexa) or fluvoxamine.⁵⁵ In the study, there was no significant difference in efficacy between the two treatment groups as measured by HAM-D. The adverse event profiles and drop-out rates were similar, but citalopram (Celexa) was generally better tolerated and induced fewer gastrointestinal adverse events than fluvoxamine.

citalopram (Celexa) versus sertraline (Zoloft)

A double-blind, randomized 24-week study evaluated the efficacy and safety of citalopram (Celexa) (mean dose 33.9 mg/day) and sertraline (Zoloft) (mean dose 82.4 mg/day) in 400 patients with MDD.⁵⁶ Response was observed using the MADRS in 60 percent of citalopram (Celexa)-treated patients and 70 percent of sertraline (Zoloft)-treated patients at week 12 (p=NS). At the conclusion of the study, response was noted in 81 percent of citalopram (Celexa) and 76 percent of sertraline (Zoloft)-treated patients (p=NS). Tolerability was comparable in the two treatment groups.

escitalopram (Lexapro) versus paroxetine (Paxil)

In a double-blind study, 459 patients with severe depression were randomized to receive escitalopram (Lexapro) 20 mg or paroxetine (Paxil) 40 mg at a fixed dose for 24 weeks.⁵⁷ From baseline to the conclusion of the study, mean change in MADRS scores, the primary endpoint, was greater with escitalopram (Lexapro) than with paroxetine (Paxil) (p<0.05). Secondary endpoints, including HAM-A, HAM-D, CGI-I, and CGI-S, also improved significantly more with escitalopram (Lexapro) (p<0.05 for all comparisons to paroxetine). There was no significant between-group difference in the incidence of adverse events during treatment.

fluoxetine (Prozac) versus fluvoxamine

After a variable single-blind washout period, 100 patients with MDD were randomized to receive either fluvoxamine 100 to 150 mg/day or fluoxetine (Prozac) 20 to 80 mg/day for seven weeks.⁵⁸ Eighty-four percent of each treatment group completed the double-blind parallel-group study. Both groups demonstrated a 60 percent improvement in HAM-D-21 over the seven-week trial. There were no statistically significant differences observed between the two groups on CGI-I or CGI-S. The medications were well tolerated, with only two patients in each group withdrawing from the study because of side effects. There were differences in the side effect profiles, with fluvoxamine being associated with less nausea than fluoxetine (Prozac).

One hundred eighty-four patients with MDD were randomized to fluoxetine (Prozac) 20 mg/day or fluvoxamine 100 mg/day in a double-blind fashion.⁵⁹ Both drugs were equally effective after six weeks, and there were no statistically significant differences between them for HAM-D-21 scores. However, at week two, the percentage of HAM-D responders and improvement in CGI-I showed fluvoxamine to be more effective than fluoxetine (Prozac). Both drugs were well tolerated, and there were no marked differences in their side effect profiles, which were typical of SSRIs.

fluoxetine (Prozac) versus paroxetine (Paxil)

A randomized, double-blind trial in 78 depressed outpatients compared fluoxetine (Prozac) (40 mg/day for most patients) to paroxetine (Paxil) (30 mg/day for most patients).⁶⁰ HAM-D and MADRS scores declined for both groups, and there were no significant differences between the two groups for any efficacy criteria at the conclusion of the study. At week three, there was a statistically significant improvement in response rate for paroxetine (Paxil). Anxiety symptoms also resolved earlier for paroxetine (Paxil)-treated patients. A higher incidence of adverse effects was reported in the fluoxetine (Prozac) group (58 percent) than the paroxetine (Paxil) group (43 percent).

In a multicenter double-blind study, 128 patients with MDD underwent a one-week placebo washout period prior to being randomized to up to 12 weeks of treatment with fluoxetine (Prozac) (up to 80 mg/day), paroxetine (Paxil) (up to 50 mg/day), or placebo.⁶¹ There were no significant differences among the three treatment groups, including the placebo group, in endpoint depression (based on HAM-D-21), nor in the degree of depression improvement. There were no statistically significant differences in rates or mean numbers of adverse events between paroxetine (Paxil)-treated patients and fluoxetine (Prozac)-treated patients.

A total of 203 patients with MDD were randomized to receive paroxetine (Paxil) or fluoxetine (Prozac), each given in a fixed dose of 20 mg/day, for the first six weeks of a double-blind study.⁶² From week seven to week 12, dosing could be adjusted biweekly as required up to paroxetine (Paxil) 50 mg/day and fluoxetine (Prozac) 80 mg/day. The mean prescribed doses were paroxetine (Paxil) 25.5 mg/day and fluoxetine (Prozac) 27.5 mg/day. Both active treatments demonstrated comparable antidepressant efficacy based on HAM-D and CGI. The overall incidence of adverse effects was comparable in the two treatment groups. Constipation, dyspepsia, tremor, sweating, and abnormal ejaculation were more common in paroxetine (Paxil)-treated subjects, whereas nausea and nervousness were more frequent in fluoxetine (Prozac)-treated patients.

fluoxetine (Prozac) versus sertraline (Zoloft)

A multicenter study evaluated 108 patients with MDD who had been randomized in double-blind fashion to receive fluoxetine (Prozac) (final mean dose 28 mg/day) or sertraline (Zoloft) (final mean dose 72 mg/day) for eight weeks.⁶³ Both treatment groups showed a statistically significant

improvement from baseline at one week that was maintained until the end of treatment for the HAM-D, HAM-A, MADRS, CGI, and Q-LES-Q; there were no significant between group differences. The incidence of adverse events was approximately 40 percent for both treatments; however, patients generally rated adverse events related to sertraline (Zoloft) to be of lower severity. Sertraline (Zoloft) was considered to be better tolerated than fluoxetine (Prozac). Overall discontinuations due to therapy failure were 19.6 percent of patients in the fluoxetine (Prozac) and 9.6 percent of the sertraline (Zoloft) group.

fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft)

One hundred and eight patients with MDD and high levels of anxiety were randomized to fluoxetine (Prozac), paroxetine (Paxil), or sertraline (Zoloft) treatment in double-blind fashion.⁶⁴ Patients in all three groups demonstrated similar baseline-to-endpoint improvement in HAM-D-17 and HAM-D Anxiety/Somatization subscores. Patients from all three groups also demonstrated similar change-over-time improvement in HAM-D-17 and HAM-D-Anxiety/Somatization subscore, except at week one where fluoxetine (Prozac)- and sertraline (Zoloft)-treated patients had statistically significantly greater improvement than paroxetine (Paxil)-treated patients in the HAM-D-Anxiety/Somatization subscore. Overall, all treatments were well tolerated.

In double-blind fashion, 284 patients with MDD were randomized to treatment with fluoxetine (Prozac) 20 to 60 mg/day, paroxetine (Paxil) 20 mg daily, or sertraline (Zoloft) 50 mg daily for 10 to 16 weeks.⁶⁵ Depression improvement, assessed with the HAM-D-17, was similar among treatments ($p=0.365$). Treatments were well tolerated in most patients with no significant differences between treatments in the incidence of adverse events.

fluoxetine weekly (Prozac Weekly)

A total of 246 patients who had taken six to 52 weeks of treatment with citalopram (Celexa) (20 to 40 mg per day), paroxetine (Paxil) (20 mg per day), or sertraline (Zoloft) (50 to 100 mg per day) were switched to open-label fluoxetine (Prozac) 90 mg once weekly for 12 weeks.⁶⁶ Seventy-nine percent of patients successfully completed a switch to fluoxetine (Prozac) with 9.3 percent discontinuing due to relapse or lack of efficacy.

paroxetine (Paxil) versus paroxetine controlled release (Paxil CR)

In two double-blind, 12-week trials, 640 patients were randomized to paroxetine CR (Paxil CR) 25 to 62.5 mg/day, paroxetine (Paxil) 20 to 50 mg/day, or placebo.⁶⁷ After 12 weeks of treatment, last observation carried forward (LOCF) HAM-D response and remission rates were 56 and 37 percent for paroxetine (Paxil), 60 and 45 percent for paroxetine CR (Paxil CR), and 48 and 34 percent for placebo, respectively. Only the difference in remission rate between paroxetine CR (Paxil CR) and placebo was statistically significant ($p<0.05$). Rate of nausea was significantly lower for paroxetine CR (Paxil CR) (14 percent) than for paroxetine (Paxil) (23 percent; $p\leq 0.05$) during the first week of treatment only.

paroxetine (Paxil) versus sertraline (Zoloft)

Three hundred fifty-three patients with MDD were randomly assigned to receive 24 weeks of double-blind treatment with flexible doses of paroxetine (Paxil) (20 to 40 mg/day) or sertraline (Zoloft) (50 to 150 mg/day).⁶⁸ After eight weeks of treatment, there was a similar rate of MADRS response (63 percent) in each group. Remission rates at eight weeks were 57 and 52 percent in the paroxetine (Paxil) and sertraline (Zoloft) groups, respectively ($p=NS$). After 24 weeks of treatment, there were similar rates of responders (69 and 72 percent) and remitters (74 and 80

percent) in the paroxetine (Paxil) and sertraline (Zoloft) groups. There was a higher incidence of diarrhea in the sertraline (Zoloft) group (35 versus 15 percent). Compared to sertraline (Zoloft), there was a higher incidence of fatigue (46 versus 21 percent), decreased libido in females (nine versus two percent), micturition problems (six versus one percent), and constipation (16 versus six percent) in the paroxetine (Paxil) group ($p < 0.05$ for all comparisons).

Generalized anxiety disorder (GAD)

escitalopram (Lexapro) versus paroxetine (Paxil)

One hundred twenty-one patients with GAD were randomized to receive 24 weeks of double-blind, flexible-dose treatment with either escitalopram (Lexapro) (10 to 20 mg/day, mean dose 14.4 mg/day) or paroxetine (Paxil) (20 to 50 mg/day, mean dose 29.9 mg/day), followed by a two-week, double-blind down-titration period.⁶⁹ After 24 weeks of treatment, LOCF mean changes in HAM-A (the primary efficacy variable) were similar for the two drugs ($p = 0.13$). Significantly fewer patients withdrew from escitalopram (Lexapro) (6.6 percent) than paroxetine (Paxil) (22.6 percent; $p = 0.02$). The frequency of treatment-emergent adverse events was higher with paroxetine (Paxil) (88.7 percent) than escitalopram (Lexapro) (77 percent). Insomnia, constipation, orgasm disturbances, and decreased libido occurred more frequently in the paroxetine (Paxil) group. Diarrhea and upper respiratory tract infection were reported more frequently with escitalopram (Lexapro).

paroxetine (Paxil) versus sertraline (Zoloft)

In a parallel-group, double-blind, flexible-dose study, 55 patients with GAD were randomly assigned to receive either paroxetine (Paxil) or sertraline (Zoloft) treatment for eight weeks.⁷⁰ By intent-to-treat analysis, both paroxetine (Paxil) and sertraline (Zoloft) resulted in significant decreases in mean HAM-A scores. There were no differences between medication groups on CGI response or remission rates, and tolerability was comparable.

Social anxiety disorder (SAD)

escitalopram (Lexapro)

Patients with SAD were randomized to receive escitalopram (Lexapro) (10 to 20 mg/day) or placebo in a 12-week, double-blind trial.⁷¹ The 368-patient study showed a statistically superior therapeutic effect for escitalopram (Lexapro) compared to placebo on the primary outcome measure, LSAS ($p < 0.05$). There were significantly more responders with escitalopram (Lexapro) (54 percent) than with placebo (39 percent; $p < 0.01$).

escitalopram (Lexapro) versus paroxetine (Paxil)

Patients with a diagnosis of SAD were randomized to 24 weeks of double-blind treatment with placebo, escitalopram (Lexapro) 5 mg, escitalopram (Lexapro) 10 mg, escitalopram (Lexapro) 20 mg, or paroxetine (Paxil) 20 mg, each given daily.⁷² LOCF analysis of the primary efficacy parameter, LSAS at week 12, showed that escitalopram (Lexapro) 5 mg and 20 mg had a significantly superior therapeutic effect compared to placebo in the 839-patient study. Escitalopram (Lexapro) superiority to placebo was observed for all doses at week 12. Further improvement in LSAS scores was seen at week 24, with significant superiority over placebo for all doses of escitalopram (Lexapro); escitalopram (Lexapro) 20 mg was significantly superior to paroxetine (Paxil) 20 mg at week 24. CGI-I response rates were significantly higher for all active treatments than for placebo at week 12. Escitalopram (Lexapro) was generally well tolerated.

fluoxetine (Prozac)

In a NIMH-sponsored multicenter study, investigators randomized 295 patients with SAD to 14 weeks of treatment with fluoxetine (Prozac) (10 to 60 mg/day) or placebo, alone or in combination with group cognitive behavioral therapy (CBT).⁷³ A fifth group underwent CBT without placebo or active treatment. All active treatments were more effective than placebo in improving CGI and Brief Social Phobia Scale. CGI response rates were similar among treatment groups, ranging from 51 percent for monotherapy with either fluoxetine (Prozac) or CBT to 54 percent for combination fluoxetine (Prozac) and CBT. In the study, patients taking either fluoxetine (Prozac) or placebo had a higher rate of nausea, insomnia, and headache compared to CBT alone.

paroxetine CR (Paxil CR)

In a double-blind multicenter study, 370 patients with SAD were randomized to receive paroxetine CR (Paxil CR) 12.5 to 37.5 mg/day or placebo for 12 weeks.⁷⁴ Patients underwent a one-week placebo run-in prior to randomization. Doses could be increased by 12.5 mg/day starting at week three. Statistically significant differences in favor of paroxetine CR (Paxil CR) compared with placebo were observed in the change from baseline to week 12 in LSAS, the primary endpoint (difference -13.33, 95% CI -18.25 to -8.41, $p < 0.001$). In the CGI-I responder analysis, 57 percent of patients treated with paroxetine CR (Paxil CR) achieved response compared with 30 percent of patients treated with placebo ($p < 0.001$). A greater percentage of patients receiving paroxetine CR (Paxil CR) achieved remission compared to patients taking placebo (24 versus eight percent; $p < 0.001$). Patients receiving paroxetine CR (Paxil CR) also had significant improvements in all secondary endpoints, including CGI-S. Dropout rates due to adverse events were low and comparable in both treatment groups.

sertraline (Zoloft)

A total of 211 patients with SAD were randomly assigned to sertraline (Zoloft) 50 to 200 mg per day or placebo in a double-blind fashion.⁷⁵ At week 12, sertraline (Zoloft) produced a significantly greater reduction in LSAS compared with placebo ($p = 0.001$) and a greater proportion of responders (56 versus 29 percent; $p < 0.05$). Sertraline (Zoloft) was well tolerated, with 7.6 percent of patients discontinuing due to adverse events compared to 2.9 percent of placebo-treated patients.

Panic disorder

citalopram (Celexa) versus escitalopram (Lexapro)

Patients with panic disorder were randomly assigned to 10 weeks of double-blind treatment with citalopram (Celexa), escitalopram (Lexapro), or placebo in a 366-patient study.⁷⁶ Both escitalopram (Lexapro) and citalopram (Celexa) statistically significantly reduced panic disorder symptoms and severity at endpoint compared to placebo ($p \leq 0.05$ for both comparisons). Citalopram (Celexa) and escitalopram (Lexapro) were safe and well tolerated, with a similar incidence of the most common adverse events and discontinuation for adverse events among all three groups.

Data from a randomized prospective comparison of escitalopram (Lexapro), citalopram (Celexa), and placebo in patients with DSM-IV panic disorder were analyzed with regard to measurements of impairment of quality of life based on the concept that outcomes of treatment for panic disorder should measure more than the number of panic attacks that a patient experiences.⁷⁷ Treatment with escitalopram (Lexapro) was associated with significant improvement on all five subscales of

the Panic and Agoraphobia Scale (PAS). Citalopram (Celexa) was significantly different from placebo in three subscales. Escitalopram (Lexapro) and citalopram (Celexa) were significantly better than placebo in improving quality of life (measured by the total score of the Q-LES-Q Scale). Escitalopram (Lexapro) was superior to placebo on 12 of 16 items of the Q-LES-Q, while citalopram (Celexa) was superior on seven items.

paroxetine (Paxil) versus sertraline (Zoloft)

A double-blind study compared sertraline (Zoloft) to paroxetine (Paxil) in the acute treatment of 225 patients with panic disorder with or without agoraphobia.⁷⁸ Patients were randomly assigned to 12 weeks of sertraline (Zoloft) titrated to 50 to 150 mg/day or paroxetine (Paxil) titrated to 40 to 60 mg/day. Patients were then tapered off medication over three weeks. The primary analysis was a non-inferiority analysis of Panic and Agoraphobia Scale (PAS) scores. Secondary measures included panic attack frequency and the CGI-I. Sertraline (Zoloft) and paroxetine (Paxil) were associated with equivalent levels of improvement on the PAS total score, as well as on all secondary outcome measures. Eighty-two percent of patients taking sertraline and 78 percent of those taking paroxetine (Paxil) were CGI-I responders at endpoint. Sertraline (Zoloft) and paroxetine (Paxil) had equivalent efficacy in panic disorder. Sertraline (Zoloft) was better tolerated and associated with less clinical worsening during taper.

Obsessive-compulsive disorder (OCD)

escitalopram (Lexapro) versus paroxetine (Paxil)

A randomized, placebo-controlled, fixed-dose trial set out to determine the efficacy and tolerability of escitalopram (Lexapro) in OCD.⁷⁹ A total of 466 adults with OCD were randomized to escitalopram (Lexapro) 10 or 20 mg daily, paroxetine (Paxil) 40 mg daily, or placebo for 24 weeks. The primary efficacy endpoint was the mean change in the Y-BOCS total score from baseline to week 12. Escitalopram (Lexapro) 20 mg/day was superior to placebo on the primary and all secondary outcome endpoints, including remission, with the improvement in Y-BOCS total score seen as early as week six. Escitalopram (Lexapro) 10 mg/day and paroxetine (Paxil) were also effective on the primary scale as well as some other outcome measures. The most common adverse events in the active treatment groups were nausea, headache, and fatigue. More paroxetine (Paxil)-treated patients withdrew due to adverse events than escitalopram (Lexapro)- or placebo-treated patients.

fluoxetine (Prozac) versus sertraline (Zoloft)

Fluoxetine (Prozac) and sertraline (Zoloft) were compared in the treatment of moderate to severe OCD for six months.⁸⁰ A total of 150 patients with OCD were randomized to fluoxetine (Prozac) or sertraline (Zoloft) in double-blind fashion. Measures of primary efficacy were the Yale-Brown Obsessive-Compulsive score (Y-BOCS), NIMH Global Obsessive-Compulsive (NIMH-OC) score, and CGI-S score and improvement. Both therapies provided significant and similar improvement at six months on the Y-BOCS and NIMH-OC scale scores ($p < 0.001$). At 12 weeks, an evaluation indicated that 49 percent of sertraline (Zoloft) patients and 25 percent of fluoxetine (Prozac) patients were mildly ill or not ill on the CGI-S ($p < 0.01$). Remissions at 24 weeks were 36 and 22 percent for sertraline (Zoloft) and fluoxetine (Prozac), respectively ($p = 0.075$). Both therapies were well tolerated.

Premenstrual dysphoric disorder (PMDD)

paroxetine CR (Paxil CR)

Data were pooled from three identical three-month, multicenter, double-blind studies of the safety and efficacy of continuous dosing of paroxetine CR (Paxil CR) in management of PMDD.^{81,82,83} In these studies, 1,030 patients with PMDD were randomized to receive paroxetine CR (Paxil CR) 12.5 mg, paroxetine CR (Paxil CR) 25 mg, or placebo. Patients in each active treatment group had statistically significant improvements in VAS total scores and Sheehan Disability Scale (SDS) ($p < 0.001$ for all comparisons to placebo). CGI-I response rates were 63 and 72 percent for the paroxetine CR (Paxil CR) 12.5 and 25 mg groups, respectively (placebo, 45 percent; $p < 0.05$ for both treatment groups). A three-month double-blind extension of these three studies showed maintained improvement in SDS for both treatment groups ($p < 0.05$ for comparisons to placebo).⁸⁴ CGI-I response rates continued to be higher in the paroxetine CR (Paxil CR) 12.5 mg (59 percent) and 25 mg (69 percent) groups than in the placebo group (42 percent; $p < 0.05$ for comparisons to placebo).

Patients were randomized in double-blind fashion to receive intermittent (luteal phase) dosing of paroxetine CR (Paxil CR) 12.5 mg, paroxetine CR (Paxil CR) 25 mg, or placebo for treatment of PMDD.⁸⁵ In this multicenter study, patients in both active treatment groups had significant improvements in VAS-Total score and SDS ($p < 0.05$ for all comparisons to placebo). CGI-I response rates were significantly higher in the paroxetine CR (Paxil CR) 12.5 (57 percent) and 25 mg (68 percent) groups than in the placebo group (43 percent; $p < 0.05$ for both active treatment comparisons to placebo).

sertraline (Zoloft)

A study compared the efficacy of continuous versus intermittent sertraline (Zoloft) in women with severe premenstrual syndrome.⁸⁶ Patients ($n = 167$) were randomly assigned to three cycles of double-blind, placebo-controlled treatment with continuous (full-cycle dosing) or intermittent (luteal-phase dosing) sertraline (Zoloft). Active daily dose of sertraline (Zoloft) was 50 mg. Outcome measures were the Daily Symptom Rating Form score and patient global ratings of functioning. Both sertraline (Zoloft) groups improved significantly more than the placebo group (full cycle sertraline (Zoloft) vs. placebo, $p = 0.02$; luteal phase sertraline (Zoloft) vs. placebo, $p = 0.009$). Sertraline (Zoloft) improvement occurred within the first month of treatment. Gradual placebo improvement was similar to sertraline (Zoloft) in the third month. A history of major depression was not associated with treatment response. More sertraline (Zoloft)-treated subjects reported improved functioning in the domains of family relationships, social activities, and sexual activity.

Post-traumatic stress disorder (PTSD)

citalopram (Celexa) versus sertraline (Zoloft)

Fifty-eight patients with PTSD were randomized to citalopram (Celexa), sertraline (Zoloft), or placebo in a double-blind manner for 10 weeks.⁸⁷ All treatment groups improved significantly in total symptoms of PTSD (as measured by the Clinician-Administered PTSD Scale) and total sleep time. The sertraline (Zoloft) group showed significantly more improvement in avoidance/numbing symptoms than the other groups. Subjects on sertraline (Zoloft) reported more gastrointestinal problems, with early terminators having more insomnia. Early terminators on citalopram (Celexa) reported more fatigue and appetite changes than other treatment groups, with completers reporting more sexual dysfunction.

Bulimia nervosa

citalopram (Celexa) versus fluoxetine (Prozac)

In a single-blind study, 37 bulimic patients were randomized to receive citalopram (Celexa) or fluoxetine (Prozac).⁸⁸ At the end of treatment, both groups showed significant improvement in eating psychopathology, angry feelings and CGI. Patients in the citalopram (Celexa) group displayed a greater improvement in depressive symptoms while those receiving fluoxetine (Prozac) experienced a greater reduction in anger. Withdrawal rates were similar in the two groups.

Special Populations^{89,90,91,92,93,94,95,96,97}

Pediatrics

In 2005, the FDA approved labeling changes for all antidepressants in order to caution practitioners, patients, family members, and caregivers about an increased risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders who are taking these medications. These changes include a boxed warning for “Suicidality in Children and Adolescents” and a Medication Guide, which is to be distributed to all patients.

The black box warning states that careful consideration is given to the risk-benefit ratio of antidepressants in this patient population. Additionally, families and caregivers should be advised of the need for close observation and communication with the prescriber. The warning was based on a meta-analysis that suggested that, during the early phase of antidepressant treatment of pediatric patients, there is a slightly increased risk of suicidal ideation and behavior.⁹⁸ Investigators analyzed data from 24 placebo-controlled trials of four to 16 weeks in length that included over 4,500 patients with MDD, OCD, and GAD. While there were 209 suicide-related events, there were no completed suicides. In these studies of SSRIs [citalopram (Celexa), fluoxetine (Prozac), fluvoxamine, paroxetine (Paxil), sertraline (Zoloft)] and other second-generation antidepressants [bupropion (Wellbutrin[®]), mirtazapine (Remeron[®]), nefazodone (Serzone[®]), venlafaxine (Effexor[®])], the overall risk for suicidality was 1.95 (95% CI 1.28-2.98). The relative risk ratio for the SSRIs in depression trials was 1.66 (95% CI 1.02-2.68). Compared to placebo, the overall risk was 0.02 (95% CI 0.01-0.03) higher with antidepressant treatment. These data are consistent with a case-control study in which the probability of antidepressant use was significantly greater in those attempting suicide after hospital discharge than in those not attempting suicide.⁹⁹

More recently, investigators analyzed SSRI prescription and suicide rates among 39 million children ages five to 14 years.¹⁰⁰ During a three-year period, there were 933 suicides in these patients (0.8 per 100,000 children per year). In the counties with the lowest rate of SSRI prescriptions, however, the suicide rate was as high as 1.7 per 100,000 children per year. This difference remained significant after adjusting for income and access to mental health care. This study is consistent with the findings from two other observational studies that increasing rates of antidepressant use among adolescents were associated with stable or declining suicide rates.^{101,102}

Major depressive disorder (MDD)

Questions concerning the safety of SSRIs in the treatment of depression in children led to a meta-analysis of data from randomized, controlled trials.¹⁰³ The trials evaluated SSRIs versus placebo in participants aged five to 18 years that were published in peer-reviewed journals or that were unpublished and included in a review by the UK's Committee on Safety of Medicines. The

outcomes evaluated were remission, response to treatment, depressive symptom scores, serious adverse events, suicide-related behaviors, and discontinuation of treatment because of adverse events. Data for two published trials suggest that fluoxetine (Prozac) has a favorable risk-benefit profile. Unpublished data lent support to this finding. Published results from one trial of paroxetine (Paxil) and two trials of sertraline (Zoloft) suggest equivocal or weak positive risk-benefit profiles.¹⁰⁴ In both cases, the addition of unpublished data indicates that risk outweighs benefit. Data from unpublished trials of citalopram (Celexa) and venlafaxine (Effexor) show unfavorable risk-benefit profiles. However, published data support efficacy of citalopram (Celexa) over placebo for MDD in a double-blind randomized clinical trial over eight weeks.¹⁰⁵ A double-blind randomized trial of escitalopram (Lexapro) and placebo showed no difference at eight weeks in efficacy or in adverse event profiles.¹⁰⁶

fluoxetine (Prozac) versus Cognitive Behavioral Therapy (CBT)

A randomized, controlled trial in 439 depressed adolescent patients was conducted to evaluate the efficacy of four 12-week treatments of either fluoxetine (Prozac) alone (10 to 40 mg/day), cognitive behavioral therapy (CBT) alone, CBT with fluoxetine (Prozac) (10 to 40 mg/day), or placebo.¹⁰⁷ Placebo and fluoxetine (Prozac) alone were administered in double-blind fashion while both CBT groups were unblinded. Patients in the combination fluoxetine (Prozac) with CBT group had statistically significant improvement on the Children's Depression Rating Scale-Revised (CDRS-R) as compared to placebo ($p=0.001$). The combination of fluoxetine (Prozac) and CBT was superior as compared with fluoxetine (Prozac) alone ($p=0.02$) or CBT alone ($p=0.01$). Fluoxetine (Prozac) alone was superior to CBT alone ($p=0.01$). The rates of response for monotherapy with fluoxetine (Prozac), CBT, and placebo were 61, 43, and 35 percent, respectively. The rate of response for the combination of fluoxetine (Prozac) and CBT was 71 percent. On the CGI-I, the two fluoxetine (Prozac)-containing regimens were statistically superior to CBT and placebo. Clinically significant suicidal thinking, which was present in 29 percent of the sample at baseline, improved significantly in all four treatment groups. Fluoxetine (Prozac) with CBT showed the greatest reduction. Seven (1.6 percent) of 439 patients attempted suicide; there were no completed suicides.

sertraline (Zoloft)

Approximately 600 patients with MDD or obsessive-compulsive disorder between six and 17 years of age have received sertraline (Zoloft) in clinical trials, both controlled and uncontrolled. The adverse event profile observed in these patients was generally similar to that observed in adult studies with sertraline (Zoloft). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of sertraline (Zoloft). Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with a SSRI is to be continued long-term.¹⁰⁸

Obsessive-compulsive disorder (OCD)

fluoxetine (Prozac), fluvoxamine, paroxetine (Paxil), sertraline (Zoloft), and clomipramine (Anafranil®)

Investigators performed a meta-analysis of 12 randomized, controlled, double-blind trials of the use of four SSRIs [fluoxetine (Prozac), fluvoxamine, paroxetine (Paxil), sertraline (Zoloft)] and one TCA [clomipramine (Anafranil)] in children and adolescents with OCD.¹⁰⁹ All active treatments were superior to placebo ($p < 0.001$). Only clomipramine (Anafranil); however, was superior to each of the SSRIs [$p < 0.03$ for all comparisons of clomipramine (Anafranil) to SSRIs]. There was no significant difference between the SSRIs.

sertraline (Zoloft) versus CBT

The recent Pediatric OCD Treatment Study (POTS) was a multicenter, blinded, randomized, controlled trial of 112 adolescents with OCD.¹¹⁰ Participants were randomly assigned to receive CBT alone, sertraline (Zoloft) alone, combined CBT and sertraline (Zoloft), or placebo for 12 weeks. Ninety-seven patients (87 percent) completed the full 12 weeks of treatment. As compared with placebo, analyses indicated a significant advantage for CBT alone ($p = 0.003$), sertraline (Zoloft) alone ($p = 0.007$), and combined treatment ($p = 0.001$). Combined treatment also proved superior to CBT alone ($p = 0.008$) and to sertraline (Zoloft) alone ($p = 0.006$), which did not differ from each other. Site differences emerged for CBT and sertraline (Zoloft) but not for combined treatment, suggesting that combined treatment is less susceptible to setting-specific variations. The rate of clinical remission for the combined treatment group was 54 percent, and the rate of clinical remission for CBT alone was 39 percent. The remission rates were 21.4 percent for sertraline (Zoloft) alone and 3.6 percent for placebo. The remission rate for combined treatment did not differ from that for CBT alone ($p = 0.42$) but did differ from sertraline (Zoloft) alone ($p = 0.03$) and from placebo ($p < 0.001$). CBT alone did not differ from sertraline (Zoloft) alone ($p = 0.24$) but did differ from placebo ($p = 0.002$), whereas sertraline (Zoloft) alone did not ($p = 0.10$). The three active treatments proved acceptable and well tolerated, with no evidence of treatment-emergent harm to self or to others.

Pregnancy

With the exception of paroxetine (Paxil, Paxil CR, Pexeva), the SSRIs are Pregnancy Category C. Paroxetine (Paxil, Paxil CR, Pexeva) is Pregnancy Category D (see Contraindications/Warnings).

Due to epidemiological studies showing an increased risk of cardiovascular malformations in infants born to women who had first trimester paroxetine (Paxil) exposure, women becoming pregnant while taking paroxetine should be advised of the potential harm to the fetus. Consideration should be given to discontinuing paroxetine (Paxil) treatment or switching to another antidepressant.

Additionally, neonates exposed to SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension (PPH). Physicians should carefully consider the potential risks and benefits of treatment when treating a pregnant woman with paroxetine (Paxil) during the third trimester.

The FDA issued an advisory that prescribers and patients carefully consider the potential benefits and risks of treatment with antidepressants during pregnancy. This advisory stems from two studies of women who had been treated with antidepressants during pregnancy. In the first study,

women who stopped their antidepressant during pregnancy because they were not feeling depressed were five times more likely to have a relapse of depression during pregnancy than women who continued to take their medication.¹¹¹ In the second study, persistent pulmonary hypertension was six times more common in babies whose mothers took antidepressants after the twentieth week of pregnancy compared to babies whose mothers did not take an antidepressant.¹¹²

The American College of Obstetricians (ACOG) has recommended against the use of SSRIs during pregnancy unless treatment is absolutely required and no other options exist. This statement is the result of increasing evidence of fetal harm from exposure to SSRIs. ACOG particularly advised that paroxetine (Paxil) be discontinued if possible when patients become pregnant, noting that withdrawal symptoms should be avoided by weaning the patient off of the drug. The group acknowledges that the risks and benefits of continued therapy must be carefully weighed. They note that untreated depression during pregnancy is associated with low weight gain, sexually transmitted diseases, and substance abuse, which are also harmful to the fetus.¹¹³

A study reported that neonates exposed in utero to SSRIs during the last trimester of pregnancy may incur a self-limited manageable neonatal behavioral syndrome.¹¹⁴ The overall relative risk for neonatal behavioral syndrome in these subjects was three times higher than neonates exposed to SSRIs in the first trimester or not at all. Most of these reports involved fluoxetine (Prozac) and paroxetine (Paxil). This syndrome involves the CNS, motor, respiratory, and GI systems, is usually mild, and disappears by two weeks of age. Supportive care in special care nurseries provided the main medical management of these patients.

In a population-based cohort study, congenital malformations occurred in 4.9 percent of children born to mothers that had a prescription for an SSRI filled during pregnancy.¹¹⁵ In the cohort of 150,780 women who were not prescribed an SSRI, congenital malformations occurred in 3.4 percent of children. The rate of malformation was 6.8 percent among women who filled an SSRI prescription during the second or third month of pregnancy when the majority of organogenesis occurs.

The manufacturer of paroxetine (Paxil) and paroxetine CR (Paxil CR) recently added a statement to the labeling of these drugs to reflect the findings of a recent retrospective epidemiological study of over 3,500 pregnant women exposed to paroxetine (Paxil, Paxil CR) or other antidepressants during the first trimester.¹¹⁶ This study showed that, compared to other antidepressants, paroxetine (Paxil, Paxil CR) was associated with about twice the risk of overall major congenital malformations (OR 2.20; 95% CI 1.34-3.63) and cardiovascular malformations (OR 2.08; 95% CI 1.03-4.23). The labeling also notes that data from a Swedish birth registry indicated no increased risk for overall major malformations in 708 infants born to women exposed to paroxetine (Paxil, Paxil CR) early in pregnancy.

Elderly

The initial dose given to elderly patients should be reduced for citalopram (Celexa), escitalopram (Lexapro), and paroxetine (Paxil, Paxil CR, Pexeva) due to increases in half-life of each drug.

Contraindications/Warnings^{117,118,119,120,121,122,123,124,125}

The SSRIs are contraindicated within 14 days of administration of MAOIs. Concomitant administration has resulted in serious, sometimes fatal, serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status

changes). Some cases presented with features resembling neuroleptic malignant syndrome (NMS).

The SSRIs are contraindicated in patients taking pimozide (Orap[®]).

Thioridazine (Mellaril[®]) should not be administered within five weeks after fluoxetine (Prozac) has been discontinued; concomitant use with fluvoxamine or paroxetine (Paxil) is contraindicated.

Black box warnings

All of the SSRIs contain a boxed warning regarding an increased risk of suicidality in children and adolescents treated with antidepressants.

“Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of “an SSRI” or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4 percent, twice the placebo risk of 2 percent. No suicides occurred in these trials. “

Clinical Worsening and Suicide Risk

All of the SSRIs have a warning that patients of any age with MDD may experience a worsening of their depression and/or the emergence of suicidality or unusual change in behavior, whether or not they are taking antidepressants and that this risk may persist until significant remission occurs. In 2007, the FDA proposed that every manufacturer update the existing black box warning on the products labeling to include warnings about increased risks of suicidal thinking and behavior in young adults ages 18 to 24 during initial treatment. This statement also includes language stating that scientific data did not show this increased risk in adults older than 24, and that adults ages 65 and older taking antidepressants have a decreased risk of suicidality. The proposed warnings also emphasize that depression and certain other serious psychiatric disorders are themselves the most important causes of suicide.

Meta-analyses have been published evaluating the data collected in manufacturers' studies and other nested case-control studies and evaluations.^{126,127,128} While the incidence of suicide is rare, the evidence of a link is contradictory in the published literature. Nonetheless, the warning is important to patients, caregivers, and family for the prevention of suicide and self-inflicted harm for children and adolescents being treated with antidepressants. A recent meta-analysis has shown that the use of SSRIs, most notably paroxetine (Paxil), is connected with an increased incidence of suicide attempts per year.¹²⁹ Investigators analyzed data from more than 87,000 patients enrolled in 702 SSRI trials and found that SSRI-treated patients were nearly 2.3 times more likely to attempt suicide than patients given placebo.¹³⁰ The risk was nearly twice that of tricyclic antidepressants (TCAs) in this analysis. Another meta-analysis of over 40,000 patients in 477 randomized controlled trials did not show evidence that SSRIs increase the risk of suicide.¹³¹

There was weak evidence; however, that these drugs do increase the risk of self-harm. A case-control study of over 146,000 depressed patients did not show evidence of increased risk of suicide or self-harm with SSRIs compared with TCAs among adults.¹³² In children and adolescents, the use of SSRIs did not increase the risk of suicide but did increase the risk of self-harm by 56 percent.

An observational study funded by NIMH found that SSRIs do not increase the risk of suicide.¹³³ Researchers found that the number of suicide attempts dropped by 60 percent in adults in the first month after starting antidepressant treatment. The suicide rate continued to drop in the succeeding five months. Among the 65,103 patients studied, there were 31 suicides in the six months after starting antidepressant therapy. That rate did not change from one month after starting treatment or in subsequent months. Teens, however, did have more suicide attempts (314 per 100,000 patients) than adults (78 per 100,000 patients). For both groups, the rate was highest in the month before treatment and dropped by about 60 percent after treatment began. These data contradict the FDA analysis of pediatric trials that showed a greater risk of suicidal thinking and behavior in the first few months of antidepressant therapy (four percent) than placebo (two percent). The FDA analysis; however, did not quantify the risk of suicide before treatment.

Screening patients for bipolar disorder

Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. While not established in controlled trials, it is believed that treatment of a major depressive episode that is the initial presentation of bipolar disorder may increase the likelihood of precipitation of a mixed/manic episode.

Serotonin syndrome

In addition to the contraindication with the MAOIs, the SSRIs have a warning that potentially life-threatening serotonin syndrome can occur with SSRIs, particularly with concomitant use of serotonergic drugs (including triptans) and other drugs that impair the metabolism of serotonin.

Rash and possible allergic events

Seven percent of patients in clinical trials of fluoxetine (Prozac) developed various types of rashes and/or urticaria; approximately thirty percent of these patients were withdrawn from treatment. Rarely, systemic events related to vasculitis and including lupus-like syndrome have developed in patients with rash. Death has been reported to occur in association with these systemic events.

Drug Interactions^{134,135,136,137,138,139,140,141,142,143,144}

Activity at the cytochrome P450 system is responsible for the majority of drug-drug interactions associated with the SSRIs. All agents have varying degrees of affinity for the P450 system. The subsystems affected are CYP2D6, CYP3A4, CYP1A2, CYP2C19, and CYP2C9/10. Any drugs metabolized through these isoenzymes could potentially interact with the SSRIs. Overall, it appears that citalopram (Celexa) and escitalopram (Lexapro), followed by sertraline (Zoloft), have the lowest number of documented drug interactions.

Effect of SSRIs on CYP450 enzymes

Drug	1A2	2D6	2C9/10	2C19	3A3/4
citalopram (Celexa)	mild	moderate	mild	--	--
escitalopram (Lexapro)	--	moderate	--	--	--
fluoxetine (Prozac, Prozac Weekly, Sarafem)	mild	substantial	substantial	moderate	mild
fluvoxamine	substantial	mild	substantial	substantial	moderate
paroxetine (Paxil, Paxil CR, Pexeva)	mild	substantial	mild	--	--
sertraline (Zoloft)	mild	mild	mild	--	mild

-- = <20 percent inhibition
Mild = 20-50 percent inhibition
Moderate = 50-150 percent inhibition
Substantial = >150 percent inhibition

Fluoxetine (Prozac, Prozac Weekly, Sarafem), paroxetine (Paxil, Paxil CR, Pexeva), and sertraline (Zoloft) are all highly protein bound. This can lead to displacement interactions with other drugs, although such interactions are rarely of clinical significance.

Other drug interactions include:

Monoamine oxidase inhibitors (MAOIs) – see Contraindications/Warnings

Tricyclic antidepressants – SSRIs may increase the levels of TCAs to toxic levels. It is recommended to avoid concomitant administration of TCAs and SSRIs. For severe depression, TCAs and SSRIs have been given together. Careful monitoring should be performed.

Warfarin – Fluvoxamine can increase the warfarin concentration by up to 65 percent.¹⁴⁵ Sertraline (Zoloft) and paroxetine (Paxil, Paxil CR, Pexeva) have also been reported to increase the prothrombin time (PT), requiring close monitoring when used concomitantly. Fluoxetine (Prozac, Prozac Weekly, Sarafem), citalopram (Celexa), and escitalopram (Lexapro) do not appear to interact with warfarin.

Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.) – Serotonin release by platelets plays an important role in hemostasis. Studies have shown an association between the use of psychotropic drugs that inhibit serotonin reuptake and the occurrence of upper GI bleeds. There is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned about the concurrent use of each of these classes of drugs.

Triptans – A potential interaction could occur with all of the SSRIs. Careful monitoring should occur with co-administration. See Warnings/Contraindications.

Thioridazine (Mellaril) – Thioridazine (Mellaril) should not be administered with fluoxetine (Prozac, Prozac Weekly, Sarafem) or paroxetine (Paxil, Paxil CR, Pexeva) or within five weeks of

fluoxetine (Prozac, Prozac Weekly, Sarafem) discontinuation. QT prolongation and torsades de pointes may occur. See Warnings/Contraindications.

Adverse Effects

Drug	Wt Loss	Wt Gain	Nausea	Headache	Agitation	Insomnia	Somnolence	W/D due to AEs
citalopram (Celexa) ¹⁴⁶	nr	≥1	21 (14)	nr	3 (1)	15 (14)	18 (10)	16 (8)
escitalopram (Lexapro) ¹⁴⁷	nr	nr	15-18 (7-8)	24 (17)	nr	7-14 (4-7)	4-13 (1-7)	4-10 (2-3)
fluoxetine (Prozac, Prozac Weekly, Sarafem) ^{148, 149}	2 (1)	nr	9-22 (7-13)	21 (19)	nr	10-33 (7-22)	5-17 (2-7)	nr
fluvoxamine ¹⁵⁰	nr	nr	28.8-36.5 (6.9-10.9)	20-21.6 (18.7-23.8)	3.8-15.7 (0-8.9)	14.4-31.3 (10.4-15)	26.2-26.9 (9-9.4)	15
paroxetine (Pexeva) ¹⁵¹	nr	nr	1.9-36.3 (0-13.7)	17-18 (14-17)	1.1-5 (0.5-4)	1.3-24 (0-13)	1.9-24 (0.2-11)	9.4-20
paroxetine CR (Paxil CR) ¹⁵²	nr	nr	2.2-15 (0-0.9)	1.4-1.9 (0.2-0.9)	nr	1.5-2.3 (0)	1.4-4.3 (0-0.3)	3-13
sertraline (Zoloft) ¹⁵³	nr	nr	13-30 (3-18)	25 (23)	1-6 (0-5)	12-28 (9-11)	2-15 (0-9)	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

A withdrawal syndrome may occur when SSRIs are stopped without an appropriate taper. This syndrome is characterized by flu-like symptoms, lightheadedness or dizziness, uneasiness or restlessness, sleep and sensory disturbances, and headache. In addition to the length of time a patient has been on a drug and its potency, the half-life of an SSRI is the major determinant of the likelihood of a withdrawal reaction. Thus, the occurrence of SSRI withdrawal syndrome is highest for fluvoxamine, paroxetine (Paxil, Paxil CR, Pexeva), and venlafaxine (Effexor, Effexor XR), followed by citalopram (Celexa) and sertraline (Zoloft). With its long half-life, fluoxetine (Prozac, Prozac Weekly, Sarafem) is the least likely to cause this syndrome.

Dosages

Usual Adult Dosages (in mg/day)

Drug	MDD	Panic Disorder	GAD	SAD	PMDD	PTSD	OCD	Dosage Forms
citalopram (Celexa)	20-40							tablets: 10, 20, 40 mg oral solution: 10 mg/5 mL
escitalopram (Lexapro)	10-20		10-20					tablets: 5, 10, 20 mg oral solution: 5 mg/5 mL
fluoxetine (Prozac, Sarafem)	20-80	10-60			20-60		20-80	pulvules/capsules (Prozac): 10, 20, 40 mg pulvules/capsules (Sarafem): 10, 20 mg oral solution: 20 mg/5 mL
fluoxetine ER (Prozac Weekly)	90 mg every 7 days							capsules, delayed-release: 90 mg
fluvoxamine							50-300	tablets: 25, 50, 100 mg
paroxetine HCl (Paxil)	20-50	10-60	10-60	10-60		20-60	20-60	tablets: 10, 20, 30, 40 mg oral suspension: 10 mg/5 mL
paroxetine HCl CR (Paxil CR)	25-62.5	12.5-75		12.5-37.5	12.5-37.5			tablets, extended-release: 12.5, 25, 37.5 mg
paroxetine mesylate (Pexeva)	20-50	10-60	20-50				20-60	tablets: 10, 20, 30, 40 mg
sertraline (Zoloft)	50-200	25-200		25-200	50-150	50-200	50-200	tablets: 25, 50, 100 mg oral solution: 20 mg/mL

The daily dosage of fluoxetine when used for bulimia nervosa is 60 mg.

All of the SSRIs, except for higher dose fluvoxamine and the weekly dosage form of fluoxetine (Prozac Weekly), are taken once daily. Daily doses of fluvoxamine greater than 100 mg should be given in two divided doses.

The dosage of all of the SSRIs, except for the once-weekly form of fluoxetine (Prozac Weekly), should be reduced in patients with hepatic dysfunction.

The dose of paroxetine (Paxil, Paxil CR, Pexeva) should be reduced in patients with renal dysfunction.

Dosages - Pediatric

fluoxetine (Prozac): The dose for pediatric patients (\geq eight years) for depression is 10 to 20 mg/day. For OCD treatment for pediatric patients (\geq seven years), the dose is 10 to 60 mg/day.

fluvoxamine: Indicated for treatment of OCD in pediatric patients eight years of age and older, the initial dose is 25 mg/day. The dose is titrated between 50 and 200 mg/day.

sertraline (Zoloft): For the treatment of OCD in pediatric patients, those aged six to 12 years should be started on 25 mg/day; those aged 13 to 17 years should begin with 50 mg/day. Dosage range in pediatric clinical trials was 25 to 200 mg/day.

Summary

A recent report on data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial funded by NIMH found that 40 to 50 percent of patients respond to treatment with SSRIs and that approximately one-third of depressed patients achieve remission within 12 weeks.¹⁵⁴ While relapse rates are high (30 percent), they do respond well to dose increases. Other drugs may be added to the SSRI, including a TCA or, if there is a history of bipolar disorder, lithium.

Based on the evidence currently available, there is no significant difference in efficacy among the various SSRIs in the treatment of MDD regardless of age, sex, or comorbidities.

These agents have similar adverse event profiles with GI disturbances (constipation, diarrhea, nausea), CNS effects (dizziness, headache, insomnia, somnolence), and sexual adverse events being most commonly reported. There are differences among SSRIs in the incidence of certain adverse events, however. Paroxetine (Paxil, Paxil CR, Pexeva) tends to cause weight gain while fluoxetine (Prozac) tends to cause weight loss. Paroxetine (Paxil, Paxil CR, Pexeva) also has the highest rate of sexual adverse events. The reduction in dopamine release secondary to serotonin actions on 5HT₂ receptors can aggravate Parkinsonism. Tremors and akathisia can occur. A few cases of tardive dyskinesia (TD) have been reported in patients taking SSRIs chronically. Unlike TCAs, the SSRIs are not effective in chronic pain. While they sometimes alleviate migraines, they can also exacerbate them.

All SSRIs, if stopped abruptly, can cause discontinuation symptoms such as agitation, anxiety, confusion, headache, insomnia, sweating, vomiting, and tremor. Fluoxetine (Prozac, Prozac Weekly, Sarafem), with the longest half-life (two to seven days, after multiple doses), is least likely to cause discontinuation symptoms. The long half-life also lessens the effect of missed doses. The shorter-acting SSRI, paroxetine (Paxil, Paxil CR, Pexeva), may have a quicker onset of action but also has a higher rate of discontinuation symptoms.

The SSRIs do differ markedly in their potential to cause interactions with other drugs. Because of substantial inhibition of one or more cytochrome P450 (CYP) enzymes at therapeutic doses, fluoxetine (Prozac, Prozac Weekly, Sarafem), fluvoxamine, and paroxetine (Paxil, Paxil CR, Pexeva) have a higher risk of CYP-mediated drug-drug interactions than citalopram (Celexa), escitalopram (Lexapro), and sertraline (Zoloft), which do not substantially inhibit any CYP enzyme.¹⁵⁵ The cleanest drug interaction profiles belong to citalopram (Celexa) and escitalopram

(Lexapro), followed by sertraline (Zoloft). Escitalopram (Lexapro) is the single isomer of citalopram (Celexa).

Fluoxetine (Prozac, Prozac Weekly, Sarafem) is a relatively activating SSRI. As a result, it is best taken in the morning and may be preferable for lethargic depression. Paroxetine (Paxil, Paxil CR, Pexeva), on the other hand, is more sedating and constipating, most likely due to its anticholinergic activity. Sertraline (Zoloft) is neither activating nor sedating; it may cause loose stool.

SSRIs are the recommended first-line medications for the treatment of PTSD.¹⁵⁶ These drugs decrease the three symptom domains of concern in this syndrome – re-experiencing, avoidance/numbing, and hyperarousal.

Three of the products are approved for pediatric use: fluoxetine (Prozac), fluvoxamine, and sertraline (Zoloft). Only fluoxetine (Prozac) is FDA-approved for treatment of depression in children. Fluoxetine (Prozac), sertraline (Zoloft), and fluvoxamine are approved for treatment of OCD in children. The FDA approved revised labeling for all antidepressant drugs with a black box warning and expanded warning statements alerting health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents.

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