



## Antidepressants, Selective Serotonin Reuptake Inhibitors (SSRI) Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

Drug	Mfr	MDD	GAD	SAD	Panic Disorder	PTSD	OCD	PMDD	Bulimia Nervosa	VMS
citalopram* <sup>1</sup>	Almatica	X	--	--	--	--	--	--	--	--
citalopram (Celexa®) <sup>2</sup>	generic, Forest/Allergan	X	--	--	--	--	--	--	--	--
escitalopram (Lexapro®) <sup>3</sup>	generic, Forest/Allergan	X (≥ 12 years)	X	--	--	--	--	--	--	--
fluoxetine*† <sup>4</sup>	generic, Almatica/ Alvogen	X (≥ 8 years)	--	--	X	--	X (≥ 7 years)	--	X	--
fluoxetine <sup>†</sup> (Prozac®) <sup>5</sup>	generic, Dista	X (≥ 8 years)	--	--	X	--	X (≥ 7 years)	--	X	--
fluoxetine <sup>‡6</sup>	generic	--	--	--	--	--	--	X	--	--
fluoxetine DR <sup>7</sup>	Dr. Reddy's	X	--	--	--	--	--	--	--	--
fluvoxamine <sup>8</sup>	generic	--	--	--	--	--	X (≥ 8 years)	--	--	--
fluvoxamine ER <sup>9</sup>	generic	--	--	--	--	--	X	--	--	--
paroxetine HCl (Paxil®) <sup>10</sup>	generic, Apotex	X	X	X	X	X	X	--	--	--
paroxetine HCl controlled release (Paxil® CR) <sup>11</sup>	generic, Apotex	X	--	X	X	--	--	X	--	--
paroxetine mesylate* (Brisdelle®) <sup>12</sup>	generic, Sebela	--	--	--	--	--	--	--	--	X
paroxetine mesylate* (Pexeva®) <sup>13</sup>	Sebela	X	X	--	X	--	X	--	--	--
sertraline* <sup>14</sup>	Almatica	X	--	--	--	--	X (≥ 6 years)	--	--	--
sertraline (Zoloft®) <sup>15</sup>	generic, Pfizer/Viatris	X	--	X	X	X	X (≥ 6 years)	X	--	--

MDD = major depressive disorder; GAD = generalized anxiety disorder; SAD = social anxiety disorder; PTSD = post-traumatic stress disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; VMS = moderate-to-severe vasomotor symptoms associated with menopause

Indications are for use in adults only unless additional ages specified.

\* Approved via 505(b)(2) New Drug Application (NDA); at least some of the information required for approval comes from studies not conducted by or for the applicant

† Fluoxetine is also indicated in combination with olanzapine for the treatment of acute depressive episodes associated with bipolar I disorder in adults and pediatric patients ≥ 10 years of age and treatment resistant depression in adults. Fluoxetine monotherapy is not approved for either of the aforementioned indications. Details on the use of fluoxetine in combination may be found in another therapeutic class review of the co-formulated agent fluoxetine/olanzapine (Symbyax®).<sup>16</sup>

‡ Products approved as Abbreviated New Drug Applications (ANDAs) with a reference product of Allergan's Sarafem®, which was discontinued.<sup>17</sup>

## OVERVIEW

### Depressive Disorders

National epidemiological data among adults has reported that in 2020 the prevalence of at least 1 major depressive episode, based on Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) criteria, was approximately 21 million American adults or 8.4% of the United States (US) population.<sup>18</sup> Women experience depression more often than men. In addition, the prevalence of depression in 2020 was estimated at 4.1 million adolescents (ages 12 to 17 years). The economic burden of treating depression is substantial, but the cost of untreated depression is even higher, as demonstrated by a study evaluating the economic impact of depression in regard to medical costs, mortality costs, and workplace costs.<sup>19</sup> Patients with depression have increased loss of workdays and more physical illnesses for which they seek medical care compared to the general population.<sup>20</sup>

The US Preventive Services Task Force recommends screening for major depressive disorder in adults, including pregnant and postpartum women, and adolescents aged 12 to 18 years (both Grade B recommendations).<sup>21,22</sup> Accurate diagnosis, effective treatment, and appropriate follow-up should be in place as well. There is insufficient evidence to recommend routine screening in children aged 11 years or younger. In addition, the USPSTF recommends that clinicians provide counseling or refer pregnant or postpartum women at an increased risk for perinatal depression to receive counseling interventions (Grade B).<sup>23</sup>

A report on data from the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial funded by the National Institute of Mental Health (NIMH), found that 40% to 50% of patients respond to treatment with SSRIs and that approximately one-third of depressed patients achieve remission within 12 weeks.<sup>24</sup> While relapse rates are high (30%), patients respond well to dose increases. Other drugs may be added to the SSRI, including a tricyclic antidepressant (TCA) or lithium.

In 2016, the American College of Physicians (ACP) published depression treatment guidelines for adults.<sup>25</sup> The guidelines evaluate both nonpharmacologic and pharmacologic treatments. They recommend either cognitive behavioral therapy (CBT) or second-generation antidepressants, including SSRIs, to treat patients with MDD and further suggest that drug selection should incorporate a consideration of treatment effects, adverse effects, cost, accessibility, and patient preferences. As these guidelines are now ≥ 5 years old, ACP considers them inactive.

In 2010, the American Psychiatric Association (APA) published practice guidelines for the treatment of MDD.<sup>26</sup> These guidelines recommend an SSRI, serotonin norepinephrine reuptake inhibitors (SNRI), mirtazapine, or bupropion as appropriate for initial treatment in most patients. Data showing superiority in efficacy of one or another class of drug (monoamine oxidase inhibitors [MAOIs], TCAs, SSRIs, SNRIs, and other antidepressants including bupropion, nefazodone, trazodone, or mirtazapine) are not robust or clinically meaningful. Antidepressants differ in their adverse event profiles and safety, and these characteristics should be considered when choosing an initial therapy. Other factors to consider include drug interaction profiles, pharmacokinetics, patient preference, and historical patient response. As these guidelines are more than 5 years old, the APA considers these as legacy guidelines.

The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines on unipolar depression from 2013 and 2015 state the goal of the acute treatment phase is remission, the goal of the continuation treatment phase is relapse prevention, and the goal of maintenance treatment is prevention of both a new episode and suicide.<sup>27,28</sup> Regarding specific treatments, no single class of antidepressants has

proven to be more effective or have a more rapid onset than another; however, limited data suggest that select TCAs and venlafaxine may be slightly more effective in severely depressed hospitalized patients. Regardless, treatment selection should be based on several individual patient factors and newer antidepressants are generally tolerated better than older classes (e.g., TCAs, MAOIs). For mild episodes, they suggest non-pharmacotherapy (medication may be considered for patients with past moderate to severe episodes), while they recommend newer antidepressants for moderate and severe depression. TCAs may also be considered for severe depression. They further note that patients will not respond sufficiently to an adequate trial of a first-line therapy in  $\geq 30\%$  of episodes. In these cases, strategies for treatment include maximizing the dose, switching to another class or another drug within the class, combination therapy (e.g., multiple drugs or drug plus psychotherapy), augmentation, or other nonpharmacologic therapy (e.g., light therapy, electroconvulsive therapy in select patients). Each strategy should be individualized and has clinical caveats. For maintenance treatment, they recommend continuing treatment for at least 6 to 9 months after remission. Although no clear recommendation is made for treatment beyond that timeframe, which may extend from a few years to a lifetime, they do state that longer-term maintenance therapy is indicated in patients with a history of  $\geq 3$  episodes or high rate of recurrence.

For adolescent (ages 10 to 21 years) depression, the American Academy of Pediatrics (AAP) recommends screening youth  $\geq 12$  years annually for depression at well visits.<sup>29,30</sup> Regarding treatment, they state that primary care clinicians should use evidence-based psychotherapy or pharmacologic treatments (e.g., SSRIs, with fluoxetine having the largest volume of supportive data in this population) whenever possible and appropriate to achieve the goals of the treatment plan and should monitor for the emergence of adverse events. The treatment should be reassessed after 6 to 8 weeks; if no improvement is noted, a consultation with a specialist may be needed. Once symptoms are resolved, treatment should be continued for a full year, based on adult literature.

Reaffirmed in 2019, the American Congress of Obstetricians and Gynecologists (ACOG) recommended against the use of SSRIs during pregnancy unless treatment is absolutely required and no other options exist.<sup>31</sup> This statement is the result of increasing evidence of fetal harm, including fetal heart defects and newborn persistent pulmonary hypertension, from exposure to SSRIs, especially when the fetus is exposed to drug during the third trimester. Some of the short-term complications noted in the newborns were jitteriness, mild respiratory distress, excessively rapid respiration, weak cry, poor muscle tone, and admission to the neonatal intensive care unit. Additionally, ACOG advised to discontinue paroxetine, if possible, when patients become pregnant, noting that withdrawal symptoms should be avoided by weaning the patient off of the drug. Despite these warnings, 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. In 2009 (reaffirmed 2014), the APA and ACOG released a joint guideline on the management of depression during pregnancy.<sup>32</sup> Some patients with mild-to-moderate depression can be treated with psychotherapy alone or in combination with medications. The report discusses the need for ongoing consultation between the obstetrician-gynecologist and psychiatrist during pregnancy. The conclusion from this joint report is that antidepressant use in pregnancy is well studied, but available research has not yet adequately controlled for other factors that may influence birth outcomes.

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.<sup>33</sup> The North American Menopause Society and National Network of Depression

Centers published consensus guidelines for the treatment of perimenopausal depression.<sup>34</sup> They recommend evidence-based treatment with antidepressants, cognitive-behavioral therapy, and other psychotherapies as first-line treatment of major depressive episodes, stating that treatment selection should be based on the patient's prior experience with these agents, a drug's adverse event profile, and drug-drug interactions. They state that SSRIs and SNRIs, particularly desvenlafaxine, have been shown to improve menopause-associated symptoms, such as vasomotor symptoms, pain, depression, sleep disturbances, and night sweats.

## Anxiety Disorders

GAD affects about 2.7% of the adult US population annually (lifetime prevalence, 5.7%), and women are 60% more likely than men to be affected by anxiety over their lifetime.<sup>35</sup> 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. For GAD, the International Consensus Group on Depression and Anxiety (ICGDA) recommends SSRIs, SNRIs, TCAs, and CBT as first-line treatments.<sup>36</sup>

In the US, social anxiety disorder (SAD) is the second most common anxiety disorder behind specific phobias and affects approximately 7.1% of Americans each year (lifetime prevalence, 12.1%).<sup>37,38</sup> This disorder is characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur. For SAD, the ICGDA expert panel guidelines recommend SSRIs as first-line therapy.<sup>39</sup>

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. It is estimated that panic disorder affects 2.7% of Americans annually with a lifetime prevalence of 4.7%.<sup>40</sup> The 2009 APA treatment guidelines state that SSRIs, SNRIs, TCAs, and benzodiazepines are roughly comparable in efficacy.<sup>41</sup> SSRIs or SNRIs are frequently preferred as initial therapy due to their favorable safety and adverse effect profile. The APA does not distinguish a particular SSRI amongst those that are approved by the Food and Drug Administration (FDA) for panic disorder. As they are over 5 years old, the APA considers their practice guidelines for panic disorder as legacy guidelines.

Obsessive-compulsive disorder (OCD) is an anxiety disorder that is characterized by recurrent, unwanted thoughts (obsessions) and/or repetitive behaviors (compulsions). This disorder affects about 1.2% of the population in the US annually (lifetime prevalence, 2.3%), with women and men being affected equally.<sup>42</sup> SSRIs are preferred as a first medication trial for OCD. All SSRIs appear to be equally effective; however, individual patients may respond well to one and not to another.<sup>43</sup> As they are over 5 years old, the APA considers their practice guidelines for OCD as legacy guidelines.

Post-traumatic stress disorder (PTSD) affects 3.6% of the adult US population annually with a lifetime prevalence of 6.8%.<sup>44</sup> The symptoms of PTSD are re-experiencing the trauma, emotional numbing, avoidance, and increased arousal.<sup>45,46,47,48,49</sup> SSRIs are the recommended first-line medications for the treatment of PTSD.<sup>50</sup> The APA published guidelines on PTSD in 2004 that also include SSRIs as the backbone of pharmacologic therapy; however, as they are over 5 years old, the APA considers their practice guidelines for PTSD as legacy guidelines.<sup>51</sup>

The 2012 WFSBP guidelines recommend SSRIs, SNRIs, and pregabalin as first-line therapies for the treatment of anxiety, obsessive-compulsive, and post-traumatic stress disorders in primary care.<sup>52,53</sup> TCAs are equally effective for some disorders, but many are less well tolerated than the SSRIs and SNRIs. In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of substance abuse disorders. Although these guidelines focus on medications, non-pharmacological interventions were also considered. CBT and other variants of behavior therapy have been sufficiently investigated in controlled studies in patients with anxiety disorders, OCD, and PTSD to support them being recommended either alone or in combination with the above medications.

Regarding the treatment of anxiety disorders in pediatric patients, the American Academy of Child and Adolescent Psychiatry (AACAP) published a practice guideline on the assessment and treatment of anxiety disorders in children and adolescents in 2020.<sup>54</sup> Regarding pharmacotherapy recommendations, AACAP recommends that SSRIs should be offered to patients 6 to 18 years of age with social anxiety, generalized anxiety, separation anxiety, or panic disorder (1B). Furthermore, they suggest that the combination of CBT and an SSRI could be offered preferentially over either CBT or an SSRI alone in the same population (2C).

## **Bulimia Nervosa**

Bulimia nervosa is an eating disorder characterized by uncontrolled consumption of large amounts of food, termed binge-eating, which is often done in secret.<sup>55</sup> It is also a recurrent and frequent behavior that is followed by extreme feelings of disgust or shame, which leads to compensatory behavior of purging, fasting, and/or excessive exercise. Purging can consist of vomiting, excessive use of laxatives, or diuretics. This condition usually has comorbidities associated with it such as depression, anxiety, and/or substance abuse problems. Over time, it has been known to incur electrolyte imbalances, gastrointestinal problems, and dental problems. Fluoxetine (Prozac) is the only SSRI medication approved by the FDA for the treatment of bulimia and has been shown to reduce the episodes of binge-eating and purging behavior, and their chance of relapse.<sup>56</sup>

## **Vasomotor Symptoms (VMS) Associated with Menopause**

VMS, such as hot flashes and night sweats, often are considered the most bothersome symptoms of menopause and affect approximately 75% of women over the age of 50 years.<sup>57</sup> The Endocrine Society recommends SSRIs, SNRIs, gabapentin, or pregabalin for moderate to severe vasomotor symptoms (VMS) in patients with contraindications to hormone therapy or who choose not to use hormone therapy.<sup>58</sup> Paroxetine mesylate (Brisdelle) is the only SSRI approved to treat VMS. The American Association of Clinical Endocrinologists (AACE) states that therapeutic trials of SSRIs and possibly other nonhormonal medications (e.g., clonidine, gabapentin) may be considered for the relief of menopausal symptoms in women with no specific contraindications.<sup>59,60</sup> The American College of Obstetricians and Gynecologists (ACOG) also states SSRIs, SNRIs, clonidine, and gabapentin are effective alternatives to hormone therapy for the treatment of VMS related to menopause.<sup>61</sup> As described above, the North American Menopause Society and National Network on Depression Centers published consensus guidelines for the treatment of perimenopausal depression and recommend the use of select antidepressants for the treatment of vasomotor symptoms associated with menopause.<sup>62</sup>



## PHARMACOLOGY<sup>63,64,65,66,67,68,69,70,71,72,73,74,75,76,77</sup>

All SSRIs exhibit antidepressant action by blocking the reuptake of serotonin into presynaptic neurons. Serotonin is a regulatory neurotransmitter with generally inhibitory effects.<sup>78</sup> 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).<sup>79,80</sup> Increasing serotonin in these extended locations mediates both the therapeutic actions and side effects of the agents.

Citalopram is more selective for serotonin activity than fluoxetine, paroxetine, sertraline, fluvoxamine, and fluvoxamine ER.<sup>81</sup> Paroxetine is the next most potent and selective inhibitor of serotonin reuptake, followed by sertraline. Escitalopram is the S-enantiomer of racemic citalopram. With respect to serotonin reuptake inhibition, escitalopram is 100 times more potent than the R-enantiomer.

Differences in affinities among the SSRIs for various receptors result in differences in the secondary pharmacologic properties of these agents. It is thought that these effects on other neurotransmitters may be responsible for the differences in the adverse effect profiles of the SSRIs.<sup>82</sup>

### Pharmacologic Properties<sup>83</sup>

Drug	Serotonin reuptake inhibition	Norepinephrine reuptake inhibition	Dopamine reuptake inhibition	Muscarinic/cholinergic antagonist
citalopram	X	X (weak)	X (weak)	--
escitalopram	X	X (weak)	X (weak)	--
fluoxetine	X	X (weak)	--	X (weak)
fluvoxamine	X	--	--	--
paroxetine	X	X (weak)	X (weak)	X (weak)
sertraline	X	X (weak)	X (weak)	--

## PHARMACOKINETICS<sup>84,85,86,87,88,89,90,91,92,93,94,95,96,97,98</sup>

The SSRIs are similar in that they are slowly, but completely, absorbed from the gut with times to peak plasma concentrations ( $C_{max}$ ) of 3 to 8 hours.<sup>99</sup> SSRIs are also widely distributed throughout the body (e.g., 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.<sup>100</sup>

Drug	Protein Binding (%)	Active Metabolites (half-life)	Half-Life (days)	
			Normal	Cirrhosis
citalopram (Celexa, No trade name)	80	none	~ 1.5-2.2	~ 3
escitalopram (Lexapro)	56	none	1.1-1.4	~ 2.5
fluoxetine (Prozac, generics of Sarafem, No trade name)	≥ 95	norfluoxetine (4–16 days)	1-6	7.6
fluvoxamine	~ 80	none	0.7	1
fluvoxamine ER	~ 80	none	0.7	nr
paroxetine HCl (Paxil)	> 93	none	0.9	0.8
paroxetine HCl controlled-release (Paxil CR)	> 93	none	0.6-0.8	nr
paroxetine mesylate (Pexeva, Brisdelle)	> 93	none	1.4	nr
sertraline (Zoloft, No trade name)	98	desmethylsertraline (2–4 days)	1-1.1	2

nr = not reported

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

Citalopram, escitalopram, and sertraline 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.<sup>101,102</sup>

All SSRIs are dependent on oxidative metabolism for elimination with the resultant metabolites being primarily excreted through the urine; however, the SSRIs differ in the cytochrome p450 (CYP) enzymes that are also involved in their metabolism. There is a 100% to 150% increase in plasma levels of paroxetine when administered to patients with severe renal insufficiency.<sup>103</sup> Renal insufficiency does not affect the other SSRIs.<sup>104,105</sup>

Paroxetine controlled-release tablets are designed to delay the start of drug release until the tablets have left the stomach and to control the dissolution rate of paroxetine over 4 to 5 hours.



## CONTRAINDICATIONS/WARNINGS<sup>106,107,108,109,110,111,112,113,114,115,116,117,118,119,</sup>

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Agents in this class should not be used in patients with known hypersensitivity to the active ingredient or any component within each product's formulation.

Serotonin syndrome has been reported with SSRIs, both alone and when take concomitantly with other serotonergic agents such as triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's wort; and with drugs that impair metabolism of serotonin, especially, monoamine oxidase inhibitors (MAOIs). Classwide labeling changes to reflect this risk and standardize language were implemented in late 2016 and early 2017. 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. The SSRIs are contraindicated within 14 days of administration of MAOIs. At least 5 weeks should be allowed after stopping fluoxetine before treatment with an MAOI.

Starting SSRIs in patients being treated with medications with MAOI activity such as linezolid or intravenous (IV) methylene blue is contraindicated because of an increased risk of serotonin syndrome. The SSRI should be discontinued before initiating treatment with medications that exhibit MAOI activity. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered. In some cases, a patient already on SSRI therapy may require urgent treatment with linezolid or IV methylene blue. If acceptable alternatives to linezolid or IV methylene blue treatment are not available and the potential benefits of linezolid or IV methylene blue treatment are judged to outweigh the risks of serotonin syndrome, then the SSRI should be stopped promptly, and linezolid or IV methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or IV methylene blue, whichever comes first. Therapy with the SSRI may be resumed 24 hours after the last dose of linezolid or IV methylene blue.

The SSRIs are contraindicated in patients taking pimozide. Coadministration may increase the risk of life-threatening cardiac arrhythmias including torsade de pointes. Thioridazine should not be administered concurrently or within 5 weeks after fluoxetine has been discontinued; concomitant use with fluvoxamine, fluvoxamine ER, or paroxetine is contraindicated. Plasma levels of thioridazine may be elevated, increasing the risk of QTc interval prolongation; this may lead to serious ventricular arrhythmias such as torsade de pointes-type arrhythmias and sudden death.

Citalopram may cause dose-dependent QT interval prolongation and should not be prescribed at doses greater than 40 mg per day. Citalopram should not be used in patients with congenital long QT syndrome. Patients with congestive heart failure, bradyarrhythmias, or predisposition to hypokalemia or hypomagnesemia may be at higher risk of developing torsade de pointes. Hypokalemia and hypomagnesemia should be corrected before administering citalopram and electrolytes should be monitored as clinically indicated. However, a study found adverse consequences from dose reductions of citalopram. Investigators examined records of a cohort of 35,848 veterans following the citalopram labeling changes which resulted from this warning. They found that a citalopram dose reduction to 40 mg or less resulted in an increase in all-cause hospitalizations or death (adjusted hazard ratio [HR], 4.5; 95% confidence interval [CI], 4.1 to 5) and hospitalizations due to depression and all-cause deaths (adjusted HR, 2.2; 95% CI, 1.8 to 2.6).<sup>121</sup> Likewise, the dose reduction did not result in a decrease in

mortality (adjusted HR, 1; 95% CI, 0.8 to 1.3) or hospitalizations for arrhythmias or all-cause death (adjusted HR, 1.3; 95% CI, 1 to 1.7).

QT prolongation and ventricular arrhythmia including torsade de pointes have been reported with use of fluoxetine. Fluoxetine should be used with caution in conditions that predispose patients to arrhythmias or increase fluoxetine exposure and in patients with risk factors for QT prolongation such as congenital long QT syndrome, a previous history of QT prolongation, and a family history of long QT syndrome or sudden cardiac death. Fluoxetine must be used carefully with other conditions that predispose patients to QT prolongation and ventricular arrhythmia such as concomitant use of drugs that prolong the QT interval, hypokalemia or hypomagnesemia, recent myocardial infarction, uncompensated heart failure, bradyarrhythmias, and other significant arrhythmias. In addition, fluoxetine should be used cautiously in individuals with conditions that predispose them to increased fluoxetine exposure such as overdose, hepatic impairment, use of CYP2D6 inhibitors, poor metabolizer of CYP2D6 status, or use of other highly protein-bound drugs. Fluoxetine must also be used with caution in combination with other drugs that prolong the QT interval.

Postmarketing reports of QT prolongation have also been reported with sertraline. A trial in healthy adults demonstrated an increase in QT in patients using sertraline, correlating with serum sertraline levels; it should be used cautiously in patients with risk factors for QT prolongation.

Coadministration of alosetron and tizanidine is contraindicated with fluvoxamine and fluvoxamine ER. The plasma concentrations of these agents may be elevated, increasing the pharmacologic and adverse effects.

Sertraline oral concentrate is contraindicated with disulfiram use due to the alcohol content of the concentrate.

## **Boxed Warnings**

All antidepressants, including the SSRIs, carry a boxed warning regarding an increased risk of suicidality in children and adolescents treated with antidepressants. This was a result of short-term studies, which were evaluating the effectiveness of the SSRIs in treating MDD, that demonstrated an increase in the risk of suicidal behavior and thinking in children and adolescents during the first few months after starting treatment. Later, a statement was added to the existing boxed warning concerning the increased risk of suicidal thinking and behavior during initial therapy in young adults ages 18 to 24 years. The recommendation for providers is to closely monitor for any symptoms of suicidal thinking, suicidal behavior, or clinical worsening of MDD in children, adolescents, and young adults starting treatment with the SSRIs.

## **Clinical Worsening and Suicide Risk**

Even though the risk of suicidal behavior and thoughts is greater in children, adolescents, and young adults, labeling for all SSRIs warn that patients of any age can experience worsening of MDD, suicidal thoughts, and suicidal behavior. Despite this warning, a statement was also included which presented scientific data demonstrating that the use of the antidepressants did not show an increased risk of suicidal behavior or thoughts in adults older than 24 years, and that adults ages 65 years and older have a decreased risk of suicidality. The warnings also emphasize that depression and certain other serious psychiatric disorders are themselves the most likely causes of suicide.

Meta-analyses have been published evaluating the data collected in manufacturers' studies and other nested case-control studies and evaluations.<sup>122,123,124</sup> 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 meta-analysis has shown that the use of SSRIs, most notably paroxetine, is connected with an increased incidence of suicide attempts per year.<sup>125</sup> 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.<sup>126</sup> The risk was nearly twice that of TCAs in this analysis. Another meta-analysis of over 40,000 patients in 477 randomized controlled trials did not show evidence that SSRIs increased the risk of suicide.<sup>127</sup> 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.<sup>128</sup> 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%. A meta-analysis of a fluoxetine trial database (18 trials) in adults with MDD reported that fluoxetine treatment did not result in greater worsening, but it was associated with greater improvement and faster resolution of ideation ( $p \leq 0.05$  versus placebo).<sup>129</sup>

An observational study funded by NIMH found that SSRIs do not increase the risk of suicide.<sup>130</sup> Researchers found that the number of suicide attempts dropped by 60% in adults in the first month after starting antidepressant treatment. The suicide rate continued to drop in the succeeding 5 months. Among the 65,103 patients studied, there were 31 suicides in the 6 months after starting antidepressant therapy. The rate did not change from 1 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% 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 (4%) than placebo (2%). 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 or hypomanic episode. The SSRIs are not FDA-approved for use in treating bipolar depression.

## Serotonin Syndrome or Neuroleptic Malignant Syndrome

In addition to the contraindication with the MAOIs, the SSRIs have a warning that potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions can occur with SSRIs, particularly with concomitant use of serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's wort) and other drugs that impair the metabolism of serotonin. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea).

## **Rash and Possible Allergic Events**

Seven percent of patients in clinical trials of fluoxetine developed various types of rashes and/or urticaria; approximately 30% of these patients withdrew 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.

## **Hyponatremia**

Several cases of hyponatremia have been reported and appeared to be reversible when SSRI therapy was discontinued. Some cases were possibly caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Those at increased risk are elderly individuals, patients taking diuretics, or who were otherwise volume depleted.

## **Hepatic and Renal Impairment**

Because many SSRIs are metabolized by the liver and excreted by the kidneys, lower or less frequent dosing may be warranted in patients with moderate to severe hepatic or renal impairment.

## **Bleeding**

SSRIs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may increase this risk.

## **Seizures**

Although not systematically evaluated, seizures have been reported infrequently in patients treated with SSRIs. These agents should be used with caution in patients with a history of seizure disorder.

## **Narrow-Angle Glaucoma**

Mydriasis has been reported in association with fluoxetine, paroxetine, and sertraline. Use with caution in patients with increased intraocular pressure or at risk of acute narrow-angle glaucoma. Antidepressants can cause pupillary dilation which may trigger an angle closure glaucoma attack in patients with anatomically narrow angles who do not have a patent iridectomy. The labels of most antidepressants, including all SSRIs, carry this warning.

## **Bone Fracture**

Exposure to some antidepressants, including SSRIs, has been associated with fractures. While there are multiple potential causes for this, it is unknown if fracture risk is attributable to SSRIs.

## **Discontinuation of Therapy**

The dosage of SSRIs should be reduced gradually whenever possible since adverse events may occur upon abrupt discontinuation. The events are generally self-limiting and include the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, insomnia, hypomania, tinnitus, and seizures.

## **Other**

SSRIs have been associated with sexual dysfunction including decreased libido, ejaculatory disturbance, impotence, and orgasmic disturbances, in males and females.

False-positive benzodiazepine urine immunoassay screening tests have been reported in patients taking sertraline.

Sertraline capsules contain FD&C Yellow No. 5 (tartrazine); exposure in susceptible individuals may cause allergic-type reactions, including bronchial asthma.

## DRUG

### INTERACTIONS<sup>131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150</sup>

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.

There are conflicting data regarding a potential reduced efficacy of tamoxifen when co-administered with paroxetine (Paxil, Paxil CR, Pexeva, Brisdelle,) due to paroxetine's irreversible inhibition of CYP2D6. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

#### Effect of SSRIs on CYP450 Enzymes

Drug	CYP1A2	CYP2D6	CYP2C9	CYP2C19	CYP3A4
citalopram	--	mild	--	--	--
escitalopram	--	moderate	--	--	--
fluoxetine	--	substantial	substantial	moderate	mild
fluvoxamine	substantial	mild	substantial	substantial	moderate
paroxetine	--	substantial	--	--	--
sertraline	--	mild	--	--	--

-- = < 20% inhibition; mild = 20% to 50% inhibition; moderate = 50% to 150% inhibition; substantial = > 150% inhibition

Fluoxetine, paroxetine, and sertraline are all highly protein bound. This can lead to displacement interactions with other drugs, although such interactions are rarely of clinical significance.

Citalopram doses greater than 20 mg per day are not recommended for patients that are taking concomitant CYP2C19 inhibitors (e.g., cimetidine) because these factors lead to increased blood levels of citalopram, thereby increasing the risk of QT interval prolongation and torsade de pointes.

The risk of QT prolongation with select SSRIs (e.g., citalopram, fluoxetine, sertraline) is increased in patients taking other agents known to prolong the QT interval (e.g., select antipsychotics, antibiotics, antiarrhythmics); concomitant use should be avoided.

Other drug interactions include the following:

Monoamine oxidase inhibitors (MAOIs) – See Contraindications/Warnings.

TCAs – SSRIs may increase the levels of TCAs to toxic levels. It is recommended to avoid concomitant administration of TCAs and SSRIs, except in cases of severe depression when concomitant administration of TCAs and SSRIs is necessary. Due to the potential to increase TCAs to toxic levels, careful monitoring

should be performed when concomitant administration is utilized.

**Serotonergic drugs** – Drugs that affect the serotonergic transmitter systems (amphetamines, linezolid, methylene blue, lithium, tramadol, St. John’s wort, and SNRIs) can interact with SSRIs and increase the risk of the occurrence of a serotonin syndrome. See Contraindications/Warnings.

**Warfarin, antiplatelets, and anticoagulants** – Fluvoxamine and fluvoxamine ER can increase warfarin concentration between 65% and 98%.<sup>151</sup> Sertraline and paroxetine/CR have also been reported to increase the prothrombin time (PT), requiring close monitoring when used concomitantly. No interactions between warfarin and fluoxetine, citalopram, or escitalopram have been reported; however, patients receiving warfarin therapy should be carefully monitored when these agents are initiated or discontinued.

The SSRIs and SNRIs may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of any SSRI or SNRI and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

**Triptans** – A potential interaction leading to serotonin syndrome can occur with all SSRIs. Careful monitoring should be performed with coadministration. See Contraindications/Warnings.

**Thioridazine** – Thioridazine should not be administered with fluoxetine, fluvoxamine, or paroxetine products, or within 5 weeks of fluoxetine discontinuation. QT prolongation and torsades de pointes may occur. See Contraindications/Warnings.

**Phenytoin/fosphenytoin (Dilantin)** – Sertraline may affect phenytoin concentrations, particularly as a narrow therapeutic index agent; additional monitoring is recommended.

**Ramelteon (Rozerem)** – Should not be used in combination with fluvoxamine/ER due to increased exposure to ramelteon.

**Tamoxifen** – May need to avoid concomitant use with paroxetine (Paxil, Paxil CR, Pexeva, Brisdelle) due to possible reduced tamoxifen efficacy. See Contraindications/Warnings.



## ADVERSE EFFECTS<sup>152,153,154,155,156,157,158,159,160,161,162,163,164,165,166</sup>

Drug	Weight Loss	Weight Gain	Nausea	Headache	Agitation	Insomnia	Somnolence	W/D due to AEs
citalopram <sup>i</sup> (Celexa)	≥ 1	≥ 1	21 (14)	nr	3 (1)	15 (14)	18 (10)	16 (8)
escitalopram (Lexapro)	nr	nr	15–18 (7–8)	24 (17)	nr	9–12 (4–6)	6–13 (2–7)	4–10 (2–4)
fluoxetine (Prozac, Sarafem, No trade name)	2–3 (1)	nr	12–29 (7–13)	13–24 (11–21)	reported	9–33 (7–22)	5–17 (2–7)	nr
fluvoxamine	≥ 1	≥ 1	40 (14)	22 (20)	2 (1)	21 (10)	22 (8)	22
fluvoxamine ER	2 ( $< 1$ )	reported	34–39 (11–13)	32–35 (30–31)	2–3 ( $< 1$ )	32–35 (13–20)	26–27 (9–11)	19–26
paroxetine (Paxil, Pexeva, Brisdelle)	reported	reported	19–26 (5–17)	17–18 (14–17)	3–5 (1–4)	18–24 (6–16)	19–24 (5–11)	9.4–16.1
paroxetine CR (Paxil CR)	1–5	1–5	17–23 (2–17)	15–27 (12–20)	1–5	7–20 (2–11)	3–22 ( $< 1$ –12)	3–13
sertraline <sup>i</sup> (Zoloft)	reported	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 or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

**\* Adverse effects reported for capsules are based on data from other formulations.**

If a patient needs to discontinue SSRI treatment, tapering the dose gradually is recommended. The patient should be monitored during discontinuation for signs of emergent adverse events such as emotional lability and worsening of depression. Otherwise, a withdrawal syndrome may occur when SSRIs are stopped without an appropriate gradual 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/ER and paroxetine/CR, followed by citalopram, and sertraline. Fluoxetine has a long half-life and as a result is the least likely to cause withdrawal symptoms.

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, SSRIs have been associated with sexual dysfunction in males and females, including decreased libido, ejaculatory disturbance, impotence, and orgasmic disturbances. Paroxetine/CR has the highest reported incidence of abnormal ejaculation. Priapism has been reported with all SSRIs. Symptoms of sexual dysfunction occasionally persist after discontinuation of fluoxetine treatment.



## SPECIAL POPULATIONS<sup>167,168,169,170,171,172,173,174,175,176,177,178,179,180,181</sup>

### Pediatrics

Fluoxetine (Prozac) is indicated for treatment of MDD in pediatric patients  $\geq 8$  years old, OCD for children  $\geq 7$  years old, and depressive episodes associated with bipolar I disorder in pediatric patients  $\geq 10$  years old in combination with olanzapine. Escitalopram (Lexapro) is approved for MDD for adolescents  $\geq 12$  years old. Sertraline (Zoloft) is indicated for treatment of OCD in children 6 years of age and older and fluvoxamine for children 8 years of age and older.

The FDA approved labeling were revised 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, adolescents and young adults 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 boxed 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 which suggested that during the early phase of antidepressant treatment of pediatric patients there is a slightly increased risk of suicidal ideation and behavior.<sup>182</sup> Investigators analyzed data from 24 placebo-controlled trials, each 4 to 16 weeks in length, which included over 4,500 patients with MDD, OCD, and GAD who were treated with SSRIs or other second generation antidepressants. There were 209 suicide-related events reported, but none were completed suicides. In these studies of SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and other second-generation antidepressants (bupropion, mirtazapine, nefazodone, venlafaxine), the overall risk for suicidality was 1.95 (95% CI, 1.28 to 2.98). The relative risk ratio for the SSRIs in depression trials was 1.66 (95% CI, 1.02 to 2.68). The overall risk was higher with antidepressant treatment when compared to placebo and was reported as 0.02 (95% CI, 0.01 to 0.03). These data are consistent with a case-controlled study in which the probability of a suicide attempt occurring in patients after hospital discharge was greater in those on an antidepressant.<sup>183</sup>

There is also evidence that SSRI use in pediatrics may lead to lower suicide rates, but it is difficult to establish a causal relationship. Researchers conducted a study that investigated the relationship between SSRI prescription use and suicide rates among 39 million children ages 5 to 14 years.<sup>184</sup> The researchers used data that was reported nationally via county level associations. During a 3-year period, there were 933 suicides in these patients (0.8 per 100,000 children per year) with the suicide rate as high as 1.7 per 100,000 children per year in the counties with the lowest rate of SSRI prescriptions dispensed and as low as 0.7 per 100,000 in counties with the highest rate of SSRI prescriptions. This reported difference remained significant after adjusting for income and access to mental health care. Unlike the studies supporting the boxed warnings, this study was consistent with the data from 2 other observational studies, which demonstrated increasing rates of antidepressant use among adolescents were associated with stable or declining suicide rates.<sup>185,186</sup>

## Pregnancy

Fluoxetine (No trade name, generics of Sarafem, fluoxetine DR) and fluvoxamine ER are Pregnancy Category C. Paroxetine is Pregnancy Category D; paroxetine can cause fetal harm when administered to a pregnant woman. Paroxetine has been associated with an increased risk of cardiovascular malformations when used in the first trimester. Paroxetine mesylate (Brisdelle) is Pregnancy Category X, since menopausal VMS does not occur during pregnancy, and Brisdelle may cause fetal harm. Citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), and sertraline (Zoloft), originally assigned Pregnancy Category C, have had their labeling updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). Sertraline capsules were not assigned a Pregnancy Category based on the PLLR. Citalopram's labeling states available data have not established an increased risk of major birth defects or miscarriage, but there is a risk of pulmonary hypertension of the newborn (PPHN) and/or poor neonatal adaptation associated with the use of SSRIs. Citalopram exposure in the fetus is similar to maternal serum levels. Escitalopram's labeling states that there are no adequate and well-controlled studies in pregnant women; thus, it should only be used if the potential benefits outweigh the potential risks to the fetus. Fluoxetine's labeling states available data over several decades have not established an increased risk of miscarriage or major birth defects. While some studies of fluoxetine have reported an increased incidence in cardiovascular malformations, they did not establish a causal relationship. Fluvoxamine's labeling states available data over several decades have not established an increased risk of miscarriage or major birth defects. Epidemiologic studies of pregnant women exposed to sertraline in the first trimester suggest no difference in major birth defect risk when compared to the background rate of major birth defects. Exposure to an SSRI or SNRI late in pregnancy may lead to an increased risk of neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding, and/or persistent pulmonary hypertension of the newborn. A risk versus benefit assessment should occur for pregnant women using one of these agents in 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.<sup>187,188</sup> This advisory stems from 2 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 5 times more likely to have a relapse of depression during pregnancy than women who continued to take their medication.<sup>189</sup> In the second study, persistent pulmonary hypertension was 6 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.<sup>190</sup>

The manufacturer of paroxetine (Paxil) and paroxetine CR (Paxil CR) added a statement to the labeling of these drugs to reflect the findings of a retrospective epidemiological study of over 3,500 pregnant women exposed to paroxetine or other antidepressants during the first trimester. The study showed that, compared to other antidepressants, paroxetine was associated with about twice the risk of overall major congenital malformations (odds ratio [OR], 2.2; 95% CI, 1.34 to 3.63) and cardiovascular malformations (OR, 2.08; 95% CI, 1.03 to 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 early in pregnancy. Furthermore, additional data from a meta-analysis assessing the neonatal risk of paroxetine use during the first trimester in pregnancy help to support the warning on the paroxetine label.<sup>191</sup> The study evaluated the malformation rates associated with the use of paroxetine during the first trimester between 1985 and 2006. Results indicated that an increased risk of cardiac malformations was associated with use of paroxetine during the first trimester (OR, 1.72; 95%

CI, 1.22 to 2.42). The authors of the study did point out that detection bias may have contributed to the detection of the cardiac malformations, but also warned that the association between first-trimester exposure to paroxetine and cardiac malformations could not be completely disregarded. Despite some of the study design flaws, prescribers and patients should evaluate the benefits against the risks of continuing paroxetine treatment during pregnancy.

Another study reported that neonates exposed *in utero* to SSRIs during the last trimester of pregnancy may incur a self-limited manageable neonatal behavioral syndrome.<sup>192</sup> The overall relative risk for neonatal behavioral syndrome in these subjects was 3 times higher than neonates exposed to SSRIs in the first trimester or not at all. Most of these reports involved fluoxetine and paroxetine. This usually mild syndrome, which disappears by 2 weeks of age, involves the central nervous system (CNS), motor, respiratory, and gastrointestinal (GI) systems. Supportive care in special care nurseries provided the main medical management of these patients. 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 any SSRI during the third trimester.

A meta-analysis assessed 29 cohort studies, including 9,085,954 births, and found that the use of SSRIs was associated with an increased risk of overall major congenital anomalies (relative risk [RR], 1.11; 95% CI, 1.03 to 1.19) and congenital heart defects (RR, 1.24; 95% CI, 1.11 to 1.37).<sup>193</sup> No significant risk was observed when the group was restricted to women with psychiatric diagnoses (major congenital anomalies RR, 1.04; 95% CI, 0.95 to 1.13) and congenital heart defects (RR, 1.06; 95% CI, 0.9 to 1.26). Similar results, with significant differences overall but not significant when restricted to women with psychiatric diagnoses, were seen when broken down by the following medications: fluoxetine, paroxetine, sertraline, and citalopram.

## Elderly

The initial dose given to elderly patients should be reduced for citalopram, escitalopram, fluvoxamine/ER, and paroxetine/CR due to increases in half-life of each drug and the decline in hepatic function in this patient population.

## DOSAGES [194](#), [195](#), [196](#), [197](#), [198](#), [199](#), [200](#), [201](#), [202](#), [203](#), [204](#), [205](#), [206](#), [207](#), [208](#)

### Usual Adult Dosages (in mg/day)

Drug	MDD	GAD	SAD	Panic Disorder	PTSD	OCD	PMDD	VMS	Dosage Forms
<b>citalopram</b>	<b>20–40</b>	<b>--</b>	<b>--</b>	<b>--</b>	<b>--</b>	<b>--</b>	<b>--</b>	<b>--</b>	<b>capsules: 30 mg*</b>
citalopram (Celexa)	20–40	--	--	--	--	--	--	--	tablets: 10 mg, 20 mg, 40 mg oral solution (generic only): 10 mg/5 mL
escitalopram (Lexapro)	10–20	10–20	--	--	--	--	--	--	tablets: 5 mg, 10 mg, 20 mg oral solution (generic only): 5 mg/5 mL
fluoxetine <sup>†</sup>	--	--	--	--	--	--	20–60	--	tablets: 10 mg, 20 mg (generic only)
fluoxetine	20–80	--	--	10–60	--	20–80	--	--	tablets: 60 mg (scored)*
fluoxetine (Prozac)	20–80	--	--	10–60	--	20–80	--	--	pulvules/capsules: 10 mg, 20 mg, 40 mg tablets (generic only): 10 mg, 20 mg oral solution (generic only): 20 mg/5 mL
fluoxetine DR	90 mg every 7 days	--	--	--	--	--	--	--	capsules, delayed-release: 90 mg
fluvoxamine	--	--	--	--	--	50–300	--	--	tablets: 25 mg, 50 mg, 100 mg
fluvoxamine ER	--	--	--	--	--	100–300	--	--	capsules, extended-release: 100 mg, 150 mg
paroxetine HCl (Paxil)	20–50	20–50	20–60	10–60	20–50	20–60	--	--	tablets: 10 mg, 20 mg, 30 mg, 40 mg oral suspension: 10 mg/5 mL
paroxetine HCl CR (Paxil CR)	25–62.5	--	12.5–37.5	12.5–75	--	--	12.5–25	--	tablets, extended-release: 12.5 mg, 25 mg, 37.5 mg
paroxetine mesylate (Brisdelle)	--	--	--	--	--	--	--	7.5	capsules: 7.5 mg
paroxetine mesylate (Pexeva)	20–50	20–50	--	10–60	--	20–60	--	--	tablets: 10 mg, 20 mg, 30 mg, 40 mg
<b>sertraline</b>	<b>150–200</b>	<b>--</b>	<b>--</b>	<b>--</b>	<b>--</b>	<b>150–200</b>	<b>--</b>	<b>--</b>	<b>capsules: 150 mg, 200 mg*</b>
sertraline (Zoloft)	50–200	--	25–200	25–200	25–200	50–200	50–150	--	tablets: 25 mg, 50 mg, 100 mg oral solution (concentrate): 20 mg/mL

\* An alternative dosage form should be used for doses that cannot be created using the available strength.

† ANDAs for Sarafem

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

When used in combination with olanzapine for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression, the initial oral dosing in adults is 20 mg once daily of fluoxetine with 5 mg once daily of olanzapine. Dosing may be titrated as appropriate; however, the safety of doses > 18 mg olanzapine with 75 mg fluoxetine has not been evaluated.

Some patients with panic disorder experience an initial feeling of increased anxiety, jitteriness, shakiness, and agitation when beginning treatment with an SSRI. For that reason, the initial doses are lower than that usually prescribed to patients with depression.

All of the SSRIs are taken once daily, except for doses of fluvoxamine greater than 100 mg and the weekly dosage form of fluoxetine. Daily doses of fluvoxamine greater than 100 mg should be given in 2 divided doses with the larger dose given at bedtime if the divided daily dosage is unequal. Fluvoxamine ER is given once daily.

Fluvoxamine ER capsules and paroxetine CR tablets should not be crushed or chewed.

Citalopram doses greater than 20 mg per day are not recommended for patients greater than 60 years of age, CYP2C19 poor metabolizers, or those taking concomitant cimetidine, because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and torsade de pointes.

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

The dose of paroxetine/CR should be reduced in patients with renal dysfunction. The once-weekly form of fluoxetine is recommended to be initiated 7 days after the last daily dose of fluoxetine (Prozac) 20 mg.

Dosing regimens for PMDD may be given either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.

## **Dosages – Pediatric**

Escitalopram (Lexapro): The dose for patients greater than 12 years of age for the treatment of depression is 10 to 20 mg/day. Initial dose should begin at 10 mg/day and may be increased to a maximum of 20 mg/day if an increase of dose is deemed necessary after 3 weeks of treatment at 10 mg/day.

Fluoxetine (Prozac): The dose for patients greater than 8 years of age for treatment of depression is 10 to 20 mg/day. For OCD treatment for patients greater than 7 years of age, the dose is 10 to 60 mg/day. When used in combination with olanzapine for the treatment of depressive episodes associated with bipolar I disorder, the initial oral dosing in pediatrics 10 to 17 years of age is 20 mg once daily of fluoxetine with 2.5 mg once daily of olanzapine. Dosing may be titrated as appropriate; however, the safety of doses > 12 mg olanzapine with 50 mg fluoxetine has not been evaluated.

Fluvoxamine: Indicated for treatment of OCD in pediatric patients 8 to 17 years of age, the initial dose is 25 mg once daily administered at bedtime. The dose is titrated by 25 mg increments every 4 to 7 days up to maximum of 200 mg/day for patients less than 11 years of age, and a maximum of 300 mg/day for patients older than 11 years of age. In the pediatric population, daily doses over 50 mg should be divided; if unequal, the larger dose should be administered at bedtime. Fluvoxamine ER is not indicated in pediatric patients.

Sertraline (Zoloft): For the treatment of OCD in pediatric patients, children ages 6 to 12 years should be

started on 25 mg/day; children ages 13 to 17 years should begin with 50 mg/day. Dosage range in pediatric clinical trials was 25 to 200 mg/day.

## CLINICAL TRIALS

### Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved 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% 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 6 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 ( $\geq 65$  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. Approval of **citalopram oral capsules**, fluoxetine 60 mg tablets, paroxetine mesylate, and **sertraline oral capsules** were based upon studies of another product with the same active ingredient.<sup>209,210,211,212</sup>

### Efficacy Scales

The 2 most common methods of reporting the efficacy results of antidepressant clinical trials are response rates and remission rates. Response generally is defined as a 50% 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% while the remission rate on active drug is generally 45% to 60%. In most studies, response rates are 10% to 15% higher than the remission rate.

For MDD, 2 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 FDA 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 4 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.<sup>213</sup> 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.<sup>214</sup> Ratings are added to form an overall score (from 0 to 60). Higher overall scores indicate increasing depressive symptoms. Cut-off points include: 0 to 6 – symptoms are absent, 7 to 19 – mild depression, 20 to 34 – moderate depression, 35 to 60 – severe depression.

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

- CGI-I (Clinical Global Impression – Global Improvement) – This 3-item scale assesses the patient's improvement or worsening.<sup>215</sup>
- CGI-S (Clinical Global Impression – Severity) – This 3-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.<sup>216</sup>
- COVI (Covi Anxiety Scale) – This 3-item scale measures the severity of anxiety symptoms.<sup>217</sup> The three items that are measured are verbal report, behavior, and somatic symptoms of anxiety. The scale is very easy to administer, but due to its lack of specificity, it is recommended to be administered with other more specific scales to measure anxiety.
- 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.<sup>218</sup> 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.
- LSAS (Liebowitz Social Anxiety Scale) – 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.
- Q-LES-Q (Quality of Life Enjoyment and Satisfaction Questionnaire) – 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.<sup>219</sup>
- PAS (Panic and Agoraphobia Scale) – This is the first scale for assessing the severity of panic disorder with or without agoraphobia. Compatible with both DSM-IV and (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) 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 5 to 10 minutes.<sup>220</sup>
- 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 1 of the most frequently used measurement scales in health care research, most commonly used for the measurement of pain.<sup>221,222</sup> This scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli.

- Y-BOCS (Yale-Brown Obsessive-Compulsive Scale) – 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)*

A double-blind, 8-week study compared the efficacy of escitalopram, citalopram, and placebo.<sup>223</sup> The study involved 491 patients with ongoing MDD randomized to receive escitalopram 10 or 20 mg/day, citalopram 40 mg/day, or placebo. Escitalopram and citalopram produced significant improvement at study endpoint relative to placebo on all measures of depression. Clinical response was evaluated by MADRS, the 24-item HAM-D, CGI scales, HAM-A, and patient-rated quality-of-life scales. Escitalopram 10 mg and 20 mg groups showed similar improvement on the MADRS. Escitalopram 10 mg/day was at least as effective as citalopram 40 mg/day at study endpoint. The incidence of discontinuations due to adverse events for the escitalopram 10 mg/day group was similar to the placebo group (4.2% versus 2.5%;  $p=0.5$ ) and not different for the escitalopram 20 mg/day group and the citalopram 40 mg/day group (10.4% versus 8.8%;  $p=0.83$ ).

A double-blind, randomized study evaluated moderately to severely depressed patients, who received citalopram 20 to 40 mg/day, escitalopram 10 to 20 mg/day, or placebo for 8 weeks.<sup>224</sup> At the conclusion of the 469-patient study, significantly more patients had responded to treatment with escitalopram than with citalopram ( $p=0.021$ ) or placebo ( $p=0.009$ ), as measured by MADRS. Both active treatments were well tolerated and had a similar adverse event profile. Both citalopram- and escitalopram-treated patients had adverse event withdrawal rates of 3% to 4% which was similar to placebo.

A double-blind, randomized clinical trial was performed in which general practitioners and psychiatrists compared escitalopram 20 mg/day with citalopram 40 mg/day over 8 weeks in 280 patients with MDD (defined as MADRS score  $\geq 30$ ).<sup>225</sup> The initial MADRS score was 36.3 +/- 4.8 and 35.7 +/- 4.4 in the escitalopram and citalopram groups, respectively. The primary efficacy variable, change in mean MADRS, improved more with escitalopram (-22.4) than with citalopram (-20.3;  $p<0.05$ ). There were more MADRS responders with escitalopram (76%) than citalopram (61%;  $p<0.01$ ). Adjusted remitter rates were 56% and 44%, respectively ( $p<0.05$ ). Tolerability was similar in both groups. Significantly more patients withdrew in the citalopram group (10.6%) than in the escitalopram group (4.3%;  $p<0.05$ ).

In a double-blind, 24-week study, 357 patients with MDD were randomly assigned to treatment with escitalopram 10 mg/day or citalopram 20 mg/day.<sup>226</sup> The MADRS response rate was higher in the escitalopram group than in the citalopram group at 8 weeks (63% and 55%, respectively;  $p<0.05$ ) but not at 24 weeks (78% and 80%, respectively;  $p=\text{not significant [NS]}$ ). Both escitalopram and citalopram were

safe and well tolerated in acute and long-term treatment, and the overall adverse event profiles for the 2 drugs were similar. There were statistically significant fewer withdrawals in the escitalopram group than in the citalopram group.

A 6-week, prospective, double-blind, randomized, multicenter study compared escitalopram to citalopram in 330 adults with MDD.<sup>227</sup> Patients were randomly assigned to receive escitalopram 10 mg, citalopram 10 mg or 20 mg. The primary efficacy outcome, the mean change from baseline in MADRS total score, was significantly higher in the escitalopram group than in the 10 mg and 20 mg citalopram groups (-28.7, -20.11, and -25.19, respectively; both,  $p < 0.001$ ). In the secondary outcomes, improvements were more apparent in the severely depressed (baseline MADRS total score,  $\geq 35$ ) subgroup (-30.33, -20.87, and -26.34, respectively). Changes in the CGI-S and CGI-I scores and the rates of response and remission were significantly higher in the escitalopram group compared with the citalopram 10 mg and 20 mg groups. The prevalence of adverse events was significantly lower in the escitalopram group compared with the citalopram groups (7, 16, and 19, respectively; both,  $p < 0.05$ ).

#### ***citalopram (Celexa) versus fluoxetine (Prozac)***

General practice patients with depression were randomized to 8 weeks of treatment with citalopram or fluoxetine, both given 20 mg once daily.<sup>228</sup> 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 appeared more rapid with assessments favoring citalopram at the 2-week evaluation. Except for back pain, which occurred more frequently with citalopram, 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 or fluvoxamine.<sup>229</sup> In the study, there was no significant difference in efficacy between the 2 treatment groups as measured by HAM-D. The adverse event profiles and drop-out rates were similar, but citalopram was generally better tolerated and induced fewer gastrointestinal adverse events than fluvoxamine. It was concluded that citalopram was as effective as fluvoxamine in the treatment of unipolar major depression. Fluvoxamine is not FDA-approved for the treatment of MDD.

#### ***citalopram (Celexa) versus sertraline (Zoloft)***

A double-blind, randomized 24-week study evaluated the efficacy and safety of citalopram (mean dose 33.9 mg/day) and sertraline (mean dose 82.4 mg/day) in 400 patients with MDD.<sup>230</sup> Response was observed using the MADRS in 68% of citalopram-treated patients and 69.5% of sertraline-treated patients at week 12 ( $p = \text{NS}$ ). At the conclusion of the study, response was noted in 81% of citalopram and 75.5% of sertraline-treated patients ( $p = \text{NS}$ ). Tolerability was comparable in the 2 treatment groups.

#### ***escitalopram (Lexapro) versus paroxetine (Paxil)***

In a double-blind study, 459 patients with severe depression were randomized to receive escitalopram 20 mg or paroxetine 40 mg at a fixed dose for 24 weeks.<sup>231</sup> Baseline MADRS score were 35.2 (SD, 3.7) for the escitalopram group and 34.8 (SD, 3.8) for the paroxetine group. From baseline to the conclusion of the study, mean change in MADRS scores, the primary endpoint, was greater with escitalopram than with paroxetine ( $p < 0.05$ ). Secondary endpoints, including HAM-A, HAM-D, CGI-I, and CGI-S, also improved significantly more with escitalopram ( $p < 0.05$  for all comparisons to paroxetine). There was no significant between-group difference in the incidence of adverse events during treatment.

### ***escitalopram (Lexapro) versus placebo in pediatrics***

The efficacy in the acute treatment of MDD was evaluated in adolescents (6 to 17 years of age) in an 8-week, flexible-dose, placebo-controlled study.<sup>232</sup> Patients were randomized to escitalopram (10 to 20 mg per day; n=131) or placebo (n=133). Randomization was not stratified by age. The primary outcome, as measured by the Children's Depression Rating Scale-Revised (CDRS-R), was improvement from baseline; escitalopram did not demonstrate a significant improvement from baseline compared to placebo; however, in a *post hoc* analysis of adolescent (ages 12 to 17 years) escitalopram significantly improved CDRS-R scores compared with placebo (least squares mean difference [MD], -4.6; p=0.047).

In a prospective, double-blind, placebo-controlled trial of escitalopram in adolescents (aged 12 to 17 years) with DSM-IV-defined MDD were randomly assigned to 8 weeks of double-blind treatment with escitalopram 10 to 20 mg/day (n=155) or placebo (n=157).<sup>233</sup> The primary efficacy parameter was changed from baseline to week 8 in CDRS-R score. Mean CDRS-R score at baseline was 57.6 for escitalopram and 56 for placebo. Significant improvement was seen in the escitalopram group relative to the placebo group at endpoint in CDRS-R score (-22.1 versus -18.8; p=0.022).

### ***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 20 to 80 mg/day for 7 weeks.<sup>234</sup> Eighty-four percent of each treatment group completed the double-blind, parallel-group study. Both groups demonstrated a 60% improvement in HAM-D-21 over the 7-week trial. There were no statistically significant differences observed between the 2 groups on CGI-I or CGI-S. The medications were well tolerated with only 2 patients in each group withdrawing from the study because of adverse effects. There were differences in the adverse effect profiles with fluvoxamine being associated with less nausea than fluoxetine. Fluvoxamine is not FDA-approved for the treatment of MDD.

In another trial, 184 patients with MDD were randomized to fluoxetine 20 mg/day or fluvoxamine 100 mg/day in a double-blind fashion.<sup>235</sup> Both drugs were equally effective after 6 weeks, and there were no statistically significant differences between them for HAM-D-21 scores. However, at week 2, the percentage of HAM-D responders and improvement in CGI-I showed fluvoxamine to be more effective than fluoxetine. Both drugs were well tolerated, and there were no marked differences in their adverse effect profiles, which were typical of SSRIs. In summary, fluvoxamine and fluoxetine have similar efficacy and safety profiles in the treatment of major depressive episode; the findings of this study indicate that fluvoxamine may have a faster onset of action with respect to resolution of depressive symptoms.

### ***fluoxetine (Prozac) versus paroxetine (Paxil)***

A 6-week, randomized, double-blind trial in 78 depressed outpatients compared fluoxetine (40 mg/day for most patients) to paroxetine (30 mg/day for most patients).<sup>236</sup> HAM-D and MADRS scores declined for both groups, and there were no significant differences between the 2 groups for any efficacy criteria at the conclusion of the study. At week 3, there was a statistically significant improvement in response rate for paroxetine. Anxiety symptoms also resolved earlier for paroxetine-treated patients. A higher incidence of adverse effects was reported in the fluoxetine group (58%) than the paroxetine group (43%). The most commonly reported adverse events were nausea and vomiting in both groups.

In a multicenter double-blind study, 128 patients with MDD underwent a 1-week placebo washout period prior to being randomized to up to 12 weeks of treatment with fluoxetine (up to 80 mg/day), paroxetine (up to 50 mg/day), or placebo.<sup>237</sup> Subjects were evaluated using the HAM-D-21 and Covi

Anxiety Scale (COVI). There were no significant differences among the 3 treatment groups, including the placebo group, in endpoint depression or anxiety severity, or in the degree of depression and anxiety improvement. There were no statistically significant differences in rates or mean numbers of adverse events between paroxetine-treated patients and fluoxetine-treated patients.

A total of 203 patients with MDD were randomized to receive paroxetine or fluoxetine, each given in a fixed dose of 20 mg/day, for the first 6 weeks of a double-blind study.<sup>238</sup> From week 7 to week 12, dosing could be adjusted biweekly as required up to paroxetine 50 mg/day and fluoxetine 80 mg/day. The mean prescribed doses were paroxetine 25.5 mg/day and fluoxetine 27.5 mg/day. Both active treatments demonstrated comparable antidepressant efficacy based on HAM-D and CGI. Anxiolytic activity of the 2 drugs (COVI, State-Trait Anxiety Inventory, HAM-D) was also comparable; however, at week 1, paroxetine was found to be superior to fluoxetine in regards to agitation and psychic anxiety based on the HAM-D scale (HAM-D Agitation item,  $p < 0.05$ ; Psychic Anxiety item,  $p < 0.05$ ), but there were no differences detected after week two. The overall incidence of adverse effects was comparable in the 2 treatment groups. Constipation, dyspepsia, tremor, sweating, and abnormal ejaculation were more common in paroxetine-treated subjects, whereas nausea and nervousness were more frequent in fluoxetine-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 (final mean dose 28 mg/day) or sertraline (final mean dose 72 mg/day) for 8 weeks.<sup>239</sup> Both treatment groups showed a statistically significant improvement from baseline at 1 week that was maintained until the end of treatment for the following measures: HAM-D, HAM-A, MADRS, CGI, and Q-LES-Q; there were no significant differences between groups. The incidence of adverse events was approximately 40% for both treatments; however, patients generally rated adverse events related to sertraline to be of lower severity. Sertraline was considered to be better tolerated than fluoxetine. Overall discontinuations due to therapy failure were 19.6% of patients in the fluoxetine and 9.6% of the sertraline group.

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

One hundred and eight patients with MDD and high levels of anxiety were randomized to fluoxetine, paroxetine, or sertraline treatment in double-blind fashion.<sup>240</sup> Patients in all 3 groups demonstrated similar baseline-to-endpoint improvement in HAM-D-17 and HAM-D Anxiety/Somatization subscores. Patients from all 3 groups also demonstrated similar change-over-time improvement in HAM-D-17 and HAM-D-Anxiety/Somatization subscore, except at week 1 where fluoxetine- and sertraline-treated patients had statistically significantly greater improvement than paroxetine-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 20 to 60 mg/day, paroxetine 20 mg daily, or sertraline 50 mg daily for 10 to 16 weeks.<sup>241</sup> This study assessed these agents for efficacy and tolerability in depressed patients and the impact of baseline insomnia on outcomes. Depression improvement, assessed with the HAM-D-17, was similar among treatments ( $p = 0.365$ ). Insomnia improvement, assessed with the HAM-D sleep disturbance factor score, was similar among treatments in all patients ( $p = 0.868$ ) and in the high ( $p = 0.852$ ) and low insomnia ( $p = 0.982$ ) subgroups. Treatments were well tolerated in most patients with no significant differences among treatments in the incidence of adverse events.

### ***fluoxetine (Prozac) versus Cognitive Behavioral Therapy (CBT) in pediatrics***

The Treatment for Adolescents with Depression Study was a randomized, placebo-controlled trial of 439 adolescents with MDD.<sup>242</sup> Treatment with fluoxetine, CBT, and fluoxetine/CBT combination was evaluated in 3 stages: (1) acute (12 weeks), (2) continuation (6 weeks), and (3) maintenance (18 weeks). Response was determined by blinded independent evaluators. Among 95 patients (39.3%) who had not achieved sustained response by week 12 (29.1% fluoxetine/CBT, 32.5% fluoxetine, and 57.9% CBT), sustained response rates during stages 2 and 3 were 80% fluoxetine/CBT, 61.5% fluoxetine, and 77.3% CBT (difference was not statistically significant). Among the remaining 147 patients (60.7%) who achieved sustained response by week 12, the CBT group was more likely than the fluoxetine group to maintain sustained response through week 36 (96.9% versus 74.1%;  $p=0.007$ ). Total rates of sustained response by week 36 were 88.4% fluoxetine/CBT, 82.5% fluoxetine, and 75% CBT.

A randomized, controlled trial in 439 depressed adolescent patients was conducted to evaluate the efficacy of four, 12-week treatments of either fluoxetine alone 10 to 40 mg/day, CBT alone, CBT with fluoxetine 10 to 40 mg/day, or placebo.<sup>243</sup> Placebo and fluoxetine alone were administered in double-blind fashion while both CBT groups were unblinded. Patients in the combination fluoxetine with CBT group had statistically significant improvement on CDRS-R as compared to placebo ( $p=0.001$ ). The combination of fluoxetine and CBT was superior as compared with fluoxetine alone ( $p=0.02$ ) or CBT alone ( $p=0.01$ ). Fluoxetine alone was superior to CBT alone ( $p=0.01$ ). The rates of response for monotherapy with fluoxetine, CBT, and placebo were 61%, 43%, and 35%, respectively. The rate of response for the combination of fluoxetine and CBT was 71%. On the Clinical Global Impression (CGI) improvement responder analysis, the 2 fluoxetine-containing regimens were statistically superior to CBT and placebo. Clinically significant suicidal thinking, which was present in 29% of the sample at baseline, improved significantly in all 4 treatment groups with the combination of fluoxetine with CBT showing the greatest reduction. Seven (1.6%) of 439 patients attempted suicide, but there were not any completed suicides. The study concluded that the combination of fluoxetine and CBT offered the most favorable tradeoff between benefit and risk for adolescents with MDD.

### ***fluoxetine weekly***

A total of 246 patients who had taken 6 to 52 weeks of treatment with citalopram 20 to 40 mg per day, paroxetine 20 mg per day, or sertraline 50 to 100 mg per day were switched to open-label fluoxetine 90 mg once weekly for 12 weeks.<sup>244</sup> Efficacy measures were percentages of patients who discontinued the study for relapse and lack of efficacy and comparison of change from baseline to endpoint in scores on the modified HAM-D-17, subscales of the HAM-D-28, and the CGI-S. Seventy-nine percent of patients successfully completed a switch to fluoxetine with 9.3% discontinuing due to relapse or lack of efficacy. No significant increases were found in the HAM-D-17 total, HAM-D-28 subscores, or CGI-S score. The study concluded that fluoxetine taken once weekly appears to be well tolerated and efficacious in patients who responded to acute therapy with other SSRIs and were subsequently switched to fluoxetine once weekly for continuation/ maintenance therapy.



### ***paroxetine (Paxil) versus paroxetine controlled-release (Paxil CR)***

In 2 double-blind, 12-week trials, 640 patients were randomized to paroxetine CR 25 to 62.5 mg/day, paroxetine 20 to 50 mg/day, or placebo.<sup>245</sup> After 12 weeks of treatment, response and remission rates were 61.2% and 44% for placebo, 72.9% and 52.5% for paroxetine IR, and 73.7% and 56.2% for paroxetine CR, respectively. During the first week of treatment only, rate of nausea was significantly lower for paroxetine CR than for paroxetine (14% versus 23%;  $p \leq 0.05$ ). The study concluded that paroxetine CR is an effective and well-tolerated antidepressant exhibiting symptomatic improvement as early as week 1. Paroxetine CR is associated with low rates of early-onset nausea and dropout rates due to adverse events comparable to those of placebo.

### ***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 (20 to 40 mg/day) or sertraline (50 to 150 mg/day).<sup>246</sup> After 8 weeks of treatment, there was a similar rate of MADRS response (63%) in each group. Remission rates at 8 weeks were 57% and 52% in the paroxetine and sertraline groups, respectively ( $p = \text{NS}$ ). After 24 weeks of treatment, there were similar rates of responders (69% and 72%) and remitters (74% and 80%) in the paroxetine and sertraline groups, respectively. There was a higher incidence of diarrhea in the sertraline group (35% versus 15%). Compared to sertraline, there was a higher incidence of fatigue (46% versus 21%), decreased libido in females (9% versus 2%), micturition problems (6% versus 1%), and constipation (16% versus 6%) in the paroxetine group ( $p < 0.05$  for all comparisons).

### ***Switching SSRIs in adolescents with resistance depression***

The TORDIA (Treatment of Resistant Depression in Adolescents) study was a NIMH-sponsored, 12-week, double-blind, randomized, controlled trial of 334 patients aged 12 to 18 years with a primary diagnosis of MDD that had not responded to a 2-month initial treatment with an SSRI.<sup>247</sup> The results were intended to assist in providing guidance for the care and management of adolescent depression that persists despite treatment with an SSRI. The patients were randomized to 1 of 4 groups: (1) switching to a second, different SSRI (paroxetine, citalopram, or fluoxetine, 20 to 40 mg), (2) switching to venlafaxine ER (Effexor XR) 150 to 225 mg, (3) switching to an alternative SSRI and receiving cognitive behavioral therapy (CBT), or (4) switching to venlafaxine ER and receiving CBT. The primary outcome measures were Clinical Global Impressions-Improvement (CGI-I) score of 2 or less (much or very much improved); a decrease of at least 50% in the Children's Depression Rating Scale-Revised (CDRS-R); and change in CDRS-R over time. CBT plus a switch to either medication regimen showed a higher response rate (54.8%; 95% CI, 47 to 62) than a medication switch alone (40.5%; 95% CI, 33 to 48;  $p = 0.009$ ), but there was no difference in response rate between venlafaxine ER and a second SSRI (48.2% [95% CI, 41 to 56] versus 47% [95% CI, 40 to 55];  $p = 0.83$ ). There were no differential treatment effects on change in the CDRS-R, self-rated depressive symptoms, suicidal ideation, or on the rate of harm-related or any other adverse events. There was a greater increase in diastolic blood pressure and pulse and more frequent occurrence of skin problems during venlafaxine ER than SSRI treatment. For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of CBT and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine ER and resulted in fewer adverse effects.

## 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 (10 to 20 mg/day, mean dose 14.4 mg/day) or paroxetine (20 to 50 mg/day, mean dose 29.9 mg/day), followed by a 2-week, double-blind down-titration period.<sup>248</sup> After 24 weeks of treatment, the last observation carried forward (LOCF) mean changes in HAM-A, the primary efficacy variable, were similar for the 2 drugs ( $p=0.13$ ). Significantly fewer patients withdrew from escitalopram (6.6%) than paroxetine (22.6%;  $p=0.02$ ). The frequency of treatment-emergent adverse events was higher with paroxetine (88.7%) than escitalopram (77%). Insomnia, constipation, orgasm disturbances, and decreased libido occurred more frequently in the paroxetine group. Diarrhea and upper respiratory tract infection were reported more frequently with escitalopram.

## Social Anxiety Disorder (SAD)

### *escitalopram (Lexapro) versus paroxetine (Paxil)*

Patients with a diagnosis of SAD were randomized to 24 weeks of double-blind treatment with placebo, escitalopram 5 mg, escitalopram 10 mg, escitalopram 20 mg, or paroxetine 20 mg, each given daily.<sup>249</sup> LOCF analysis of the primary efficacy parameter, LSAS at week 12, showed that escitalopram 5 mg and 20 mg had a significantly superior therapeutic effect compared to placebo in the 839-patient study. Escitalopram 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; escitalopram 20 mg was significantly more favorable to paroxetine 20 mg at week 24. CGI-I response rates were significantly higher for all active treatments than for placebo at week 12. Escitalopram was generally well tolerated. Escitalopram is not FDA-approved for the treatment of SAD.

### *paroxetine CR (Paxil CR) versus placebo*

In a double-blind, multicenter study, 370 patients with SAD were randomized to receive paroxetine CR 12.5 to 37.5 mg/day or placebo for 12 weeks.<sup>250</sup> Patients underwent a 1-week placebo run-in prior to randomization. Doses could be increased by 12.5 mg/day starting at week 3. Statistically significant differences in favor of paroxetine 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% of patients treated with paroxetine CR achieved response compared with 30% of patients treated with placebo ( $p<0.001$ ). A greater percentage of patients receiving paroxetine CR achieved remission compared to patients taking placebo (24% versus 8%;  $p<0.001$ ). Patients receiving paroxetine 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) versus placebo*

A total of 211 patients with SAD were randomly assigned to sertraline 50 to 200 mg per day or placebo in a double-blind fashion.<sup>251</sup> At week 12, sertraline produced a significantly greater reduction in LSAS compared with placebo (mean change from baseline: -31 versus -21.7;  $p=0.001$ ) and a greater proportion of responders (56% versus 29%;  $p<0.05$ ). Sertraline was well tolerated with 7.6% of patients discontinuing due to adverse events compared to 2.9% of placebo-treated patients.



## Panic Disorder

### ***fluoxetine (Prozac) versus placebo***

Patients with a diagnosis of panic disorder (n=243) were randomly assigned to treatment with 10 or 20 mg/day of fluoxetine or placebo.<sup>252</sup> A 2-week, single-blind placebo lead-in was followed by a 10-week acute phase with random assignment to placebo, 10 mg/day of fluoxetine, or 20 mg/day of fluoxetine. Patients in the 20-mg fluoxetine treatment group received 10 mg/day of fluoxetine for the first week. Patients with clinician-rated CGI improvement score of 1 or 2 could enter a 24-week continuation phase with random assignment to continued therapy with their acute-phase dose or placebo. Fluoxetine, particularly the 20 mg/day dose, was associated with more improvement than was placebo in patients with panic disorder across multiple symptom measures, including global improvement, total panic attack frequency, phobic symptoms, and functional impairment. Global improvement was most highly correlated with reductions in overall anxiety and phobic symptoms and least correlated with reduction in panic attacks. Fluoxetine treatment for panic disorder was well tolerated.

### ***paroxetine (Paxil) versus sertraline (Zoloft)***

A double-blind study compared sertraline to paroxetine in the acute treatment of 225 patients with panic disorder with or without agoraphobia.<sup>253</sup> Patients were randomly assigned to 12 weeks of sertraline titrated to 50 to 150 mg/day or paroxetine titrated to 40 to 60 mg/day. Patients were then tapered off medication over 3 weeks. The primary analysis was a non-inferiority analysis of PAS scores. Secondary measures included panic attack frequency and CGI-I. Sertraline and paroxetine 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% of those taking paroxetine were CGI-I responders at endpoint. Sertraline and paroxetine had equivalent efficacy in panic disorder. Sertraline 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 in OCD.<sup>254</sup> A total of 466 adults with OCD were randomized to escitalopram 10 or 20 mg daily, paroxetine 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. Secondary efficacy endpoints included remission at weeks 12 and 24. Escitalopram 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 6. Escitalopram 10 mg/day and paroxetine 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-treated patients withdrew due to adverse events than escitalopram- or placebo-treated patients. Escitalopram is not FDA-approved for to treat OCD.

### ***fluoxetine (Prozac) versus sertraline (Zoloft)***

Fluoxetine and sertraline were compared in the treatment of moderate to severe OCD for 6 months.<sup>255</sup> A total of 150 patients with OCD were randomized to fluoxetine or sertraline in double-blind fashion. Measures of primary efficacy were the Y-BOCS, NIMH Global Obsessive-Compulsive (NIMH-OC) score, and CGI-S score and improvement. Both therapies provided significant and similar improvement at 6 months on the Y-BOCS and NIMH-OC scale scores (p<0.001). At 12 weeks, an evaluation indicated that

49% of sertraline patients and 25% of fluoxetine patients were mildly ill or not ill on the CGI-S ( $p < 0.01$ ). Remissions at 24 weeks were 36% and 22% for sertraline and fluoxetine, respectively ( $p = 0.075$ ). Both therapies were well tolerated.

### ***fluoxetine (Prozac) versus placebo in pediatrics***

Efficacy of fluoxetine in pediatric OCD was demonstrated in a double-blind, placebo-controlled, randomized, 13-week clinical trial in children ages 7 to 17 ( $n = 103$ ).<sup>256,257</sup> Patients were randomized 2:1 to placebo or fluoxetine. Fluoxetine doses were initiated at 10 mg/day but were increased to 20 mg/day after 2 weeks. Additional dose increases were allowed for initial non-responders up to 60 mg/day. Fluoxetine was associated with a greater improvement in Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) compared to placebo ( $p = 0.026$ ).

### ***fluvoxamine versus placebo in pediatrics***

Efficacy of fluvoxamine in pediatric OCD was established in a double-blind, placebo-controlled trial in OCD patients aged 8 to 17 years.<sup>258</sup> Patients were randomized to placebo or fluvoxamine 50 to 200 mg/day for 10 weeks. Fluvoxamine was associated with a greater improvement in CY-BOCS compared to placebo ( $p < 0.05$ ), beginning at week 1 and sustained through week 10.

### ***sertraline (Zoloft) versus CBT in pediatrics***

The Pediatric OCD Treatment Study (POTS) was a randomized multicenter, blinded, controlled trial of 112 adolescents with OCD.<sup>259</sup> Participants were randomly assigned to receive CBT alone, sertraline alone, combination CBT and sertraline, or placebo for 12 weeks. Ninety-seven patients (87%) completed the full 12 weeks of treatment. As compared with placebo, analyses indicated a significant advantage for CBT alone ( $p = 0.003$ ), sertraline alone ( $p = 0.007$ ), and combined treatment ( $p = 0.001$ ). Combined treatment also proved superior to CBT alone ( $p = 0.008$ ) and to sertraline alone ( $p = 0.006$ ), which did not differ from each other. Site differences emerged for CBT and sertraline 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%, and the rate of clinical remission for CBT alone was 39%. The remission rates were 21.4% for sertraline alone and 3.6% for placebo. The remission rate for combined treatment did not differ from the remission rate for CBT alone ( $p = 0.42$ ) but did differ from sertraline alone ( $p = 0.03$ ) and from placebo ( $p < 0.001$ ). CBT alone did not differ from sertraline alone ( $p = 0.24$ ) but did differ from placebo ( $p = 0.002$ ). The 3 active treatments proved acceptable and well tolerated with no evidence of treatment-emergent harm to self or to others.

## **Premenstrual Dysphoric Disorder (PMDD)**

### ***fluoxetine (Sarafem) versus placebo***

In a 3 month, intermittent dosing double-blind, parallel group study patients ( $n = 260$ ) were randomized to fluoxetine 10 mg/day or 20 mg/day, or placebo.<sup>260</sup> Fluoxetine or placebo was started 14 days prior to the anticipated onset of menstruation and was continued through the first full day of menses. Fluoxetine 20 mg/day, but not 10 mg/day, was shown to be significantly more effective than placebo as measured by the Daily Record of Severity Problems (DRSP) total score.

In a 6-month, continuous dosing double-blind, parallel group study involving 320 patients, fixed doses of fluoxetine 20 and 60 mg/day given daily throughout the menstrual cycle were shown to be significantly more effective than placebo as measured by a VAS total score (including mood and physical

symptoms).<sup>261</sup> The average total VAS score decreased 7 % on placebo treatment, 36% on 20 mg, and 39% on 60 mg fluoxetine. The difference between the 20 and 60 mg doses was not statistically significant.

### ***paroxetine CR (Paxil CR) versus placebo***

Data were pooled from 3 identical, 3-month, multicenter, double-blind studies of the safety and efficacy of continuous dosing of paroxetine CR in management of PMDD.<sup>262,263,264</sup> In these studies, 1,030 patients with PMDD were randomized to receive daily paroxetine CR 12.5 mg, paroxetine 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% for the paroxetine CR 12.5 and 25 mg groups, respectively (placebo, 45%;  $p < 0.05$  for both treatment groups). A 3-month double-blind extension of the 3 studies showed maintained improvement in SDS for both treatment groups ( $p < 0.05$  for comparisons to placebo).<sup>265</sup> CGI-I response rates continued to be higher in the paroxetine CR 12.5 mg (59%) and 25 mg (69%) groups than in the placebo group (42%;  $p < 0.05$  for comparisons to placebo).

Patients were randomized in a double-blind fashion to receive intermittent (luteal phase) dosing of paroxetine CR 12.5 mg, paroxetine CR 25 mg, or placebo for treatment of PMDD.<sup>266</sup> In the 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 12.5 (57%) and 25 mg (68%) groups than in the placebo group (43%;  $p < 0.05$  for both active treatment comparisons to placebo).

### ***sertraline (Zoloft) versus placebo***

A study compared the efficacy of continuous versus intermittent sertraline in women with severe premenstrual syndrome.<sup>267</sup> Patients ( $n = 167$ ) were randomly assigned to 3 cycles of double-blind, placebo-controlled treatment with continuous (full-cycle dosing) or intermittent (luteal-phase dosing) sertraline. Active daily dose of sertraline was 50 mg. Outcome measures were the Daily Symptom Rating Form score and patient global ratings of functioning. Both sertraline groups improved significantly more than the placebo group (full cycle sertraline versus placebo,  $p = 0.02$ ; luteal phase sertraline versus placebo,  $p = 0.009$ ). There was no difference between the 2 sertraline groups ( $p = 0.76$ ). Sertraline improvement occurred within the first month of treatment. Gradual placebo improvement was similar to sertraline in the third month. A history of major depression was not associated with treatment response. More sertraline-treated subjects reported improved functioning in the domains of family relationships, social activities, and sexual activity.

To compare rates of relapse and time to relapse between short- and long-term treatment with sertraline administered in the luteal phase of the menstrual cycle, an 18-month survival study with a randomized double-blind switch to placebo after 4 or 12 months of sertraline treatment was performed in 174 patients.<sup>268</sup> The relapse rate was 41% during long-term treatment compared with 60% after short-term sertraline therapy, with a median time to relapse of 8 months versus 4 months (HR, 0.58; 95% CI, 0.34 to 0.98;  $p = 0.04$ ). Patients with severe symptoms at baseline were more likely to experience relapse compared with patients in the lower symptom severity group (HR, 2.02; 95% CI, 1.18 to 3.41;  $p = 0.01$ ) and were more likely to experience relapse with short-term treatment ( $p = 0.03$ ). Duration of treatment did not affect relapse in patients in the lower symptom severity group. Patients who demonstrated remission were least likely to experience relapse (HR, 0.22; 95% CI, 0.1 to 0.45;  $p < 0.001$ ).

## Post-traumatic Stress Disorder (PTSD)

### *paroxetine (Paxil) versus placebo*

A 12 week, double-blind, fixed-dose, placebo-controlled study evaluated the safety and efficacy of paroxetine in patients with PTSD.<sup>269</sup> Patients were selected based on DSM-IV criteria for PTSD and a score of 50 or more as determined by CAPS, part 2. These patients were randomly assigned to take placebo (n=186), paroxetine 20 mg per day (n=183), or paroxetine 40 mg per day (n=182) for a total of 12 weeks. One primary outcome measure was based on CAPS, part 2, and evaluated the change in total score from baseline during the 12-week study. The other primary outcome measure evaluated the proportion of responders who indicated a response greater than “much improved” based on the CGI improvement rating. After 12 weeks, a statistically significant difference existed in the improvement of total PTSD symptoms, re-experiencing, avoidance/numbering, and hyper arousal based on CAPS, part 2, between both doses of paroxetine versus placebo ( $p<0.001$ ). Also after 12 weeks, statistically more patients on either dose of paroxetine experienced a “much improved” to “very much improved” CGI improvement rating in comparison to placebo ( $p<0.001$ ). Overall, paroxetine was well tolerated throughout the study with less than 10% of patients experiencing asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence in comparison to 5% of the placebo treated patients. Only 9 of the 365 patients taking paroxetine during the study experienced serious adverse events, and 7 of the 9 were rated as not related to paroxetine treatment by investigators.

### *sertraline (Zoloft) versus citalopram (Celexa)*

Fifty-eight patients with PTSD were randomized to citalopram, sertraline, or placebo in a double-blind manner for 10 weeks.<sup>270</sup> All treatment groups improved significantly in total symptoms of PTSD [as measured by the Clinician-Administered PTSD Scale (CAPS)] and total sleep time. A comparison of treatment groups did not show a significant difference between them in reduction of PTSD symptoms. The sertraline group showed significantly more improvement in avoidance/numbing symptoms than the other groups. Subjects on sertraline reported more gastrointestinal problems, with early terminators having more insomnia. Early terminators on citalopram reported more fatigue and appetite changes than other treatment groups, with completers reporting more sexual dysfunction. Citalopram is not FDA-approved for the treatment of PTSD.

### *sertraline (Zoloft) versus placebo*

In a 12-week, double-blind, placebo-controlled trial preceded by a 2-week, single-blind placebo lead-in period, 187 patients with PTSD were randomized to acute treatment with sertraline in flexible daily dosages of 50 to 200 mg/d, following 1 week at 25 mg/day; or placebo.<sup>271</sup> Sertraline treatment yielded significantly greater improvement than placebo on 3 of the 4 primary outcome measures (mean change for CAPS-2 total score [ $p=0.02$ ], and for CGI-S [ $p=0.01$ ]; mean CGI-I score at end point [ $p=0.02$ ]), with the fourth measure, the Impact of Event Scale (IES) total score, showing a trend toward significance ( $p=0.07$ ). Treatment with sertraline resulted in a responder rate of 53% at study end point compared with 32% for placebo ( $p=0.008$ ). Sertraline had significant efficacy compared to placebo on the CAPS-2 PTSD symptom clusters of avoidance/numbing ( $p=0.02$ ) and increased arousal ( $p=0.03$ ) but not on re-experiencing/intrusion ( $p=0.14$ ). Sertraline was well tolerated, with insomnia the only adverse effect reported significantly more often than placebo (16% versus 4.3%;  $p=0.01$ ).

## Bulimia Nervosa

### *citalopram (Celexa) versus fluoxetine (Prozac)*

In a single-blind study, 37 bulimic patients were randomized to receive citalopram or fluoxetine.<sup>272</sup> Patients were assessed on clinical, psychopathological, personality, and CGI measures. At the end of treatment, both groups showed significant improvement in eating psychopathology, angry feelings, and CGI. Patients in the citalopram group displayed a greater improvement in depressive symptoms while those receiving fluoxetine experienced a greater reduction in anger. Withdrawal rates were similar in the 2 groups. Citalopram is not FDA-approved for the treatment of bulimia nervosa.

## Vasomotor Symptoms Associated with Menopause

### *paroxetine mesylate (Brisdelle) versus placebo*

Paroxetine mesylate (7.5 mg once daily at bedtime) was studied in 2 randomized, double-blind, placebo-controlled trials, of 12 and 24 weeks duration, in a total of 1,175 women with moderate-to-severe VMS.<sup>273</sup> Enrolled patients had at least 7 to 8 moderate-to-severe hot flashes per day ( $\geq 50$  per week) for at least 30 days preceding randomization. In study 1, the median frequency of moderate-to-severe events was significantly decreased at 12 weeks compared to baseline (4 weeks: paroxetine -4.3 versus placebo -3.1 [difference between median changes from baseline, -1.2;  $p < 0.01$ ]; 12 weeks: paroxetine -5.9 versus placebo -5 [difference, -0.9;  $p < 0.01$ ]). In this study, the reduction in severity was significant in favor of paroxetine at 4 weeks; the difference did not reach statistical significance at 12 weeks. In the second study, paroxetine significantly reduced the frequency of moderate-to-severe events at 4 and 12 weeks compared to placebo; the treatment differences reported were similar to those in the first study, -1.3 and -1.7 at 4- and 12-weeks, respectively. The study demonstrated the reduction in severity favored paroxetine at both time points (4 weeks: median treatment difference, -0.03 [ $p = 0.04$ ]; 12 weeks: difference, -0.05 [ $p < 0.01$ ]).

## META-ANALYSES

### Major Depressive Disorder

A meta-analysis that included 13 pediatric MDD trials with a total of 3,004 patients indicated that the greatest benefits of SSRIs in pediatric patients occurred early in treatment. There were no significant differences based on maximum dose or between SSRI agents. SSRIs were demonstrated to have a smaller benefit in pediatric patients compared to adults.<sup>274</sup>

A network meta-analysis evaluated the efficacy of antidepressants compared to placebo for MDD in children and adolescents and found, with exception of fluoxetine, that none were statistically superior to placebo (34 trials;  $n = 5,260$ ).<sup>275</sup> This meta-analysis included inpatients and outpatients exposed to 1 of 14 different medications, including 5 SSRIs (fluoxetine, paroxetine, citalopram, sertraline, and escitalopram) or placebo, and trials were done both in and outside of the US with ages ranging from 6 to 18 years. Only fluoxetine demonstrated efficacy compared to placebo in depression symptom improvement as measured using a pre-defined system accounting for scores on rating scales from the clinical trials (standardized MD, -0.51; 95% CI, -0.99 to -0.3). Other antidepressants, but not any of the SSRIs, were also associated with reduced tolerability compared to placebo. Only fluoxetine or escitalopram are approved for children and/or adolescents with MDD. A subsequent systematic review and network meta-analysis (71 trials;  $n = 9,510$ ) of available treatment interventions for children and



adolescents with MDD also found that fluoxetine, alone or in combination with select psychotherapy, appears to be the best choice; however, study authors caution that high-quality data are very limited.<sup>276</sup>

A Cochrane network meta-analysis of new generation antidepressants for depression in children and adolescents (ages 6 to 18 years of age) assessed the efficacy of SSRIs, SNRIs, bupropion, and mirtazapine (26 studies).<sup>277</sup> Data were lacking to determine the impact on depressive episode resolution and completed suicides, but reduction in depressive symptoms was evaluable. Compared to placebo, most included antidepressants may be associated with a small and unimportant reduction in depression symptoms, as measured by a score range of 17 to 113 on the CDRS-R scale. Those with a high certainty of evidence included paroxetine (MD, -1.43; 95% CI, -3.9 to 1.04; NS), vilazodone (MD, -0.84; 95% CI, -3.03 to 1.35; NS), and desvenlafaxine (MD, -0.07; 95% CI, -3.51 to 3.36; NS), and moderate certainty evidence supported sertraline (MD, -3.51; 95% CI, -6.99 to -0.04), fluoxetine (MD, -2.84; 95% CI, -4.12 to -1.56), and escitalopram (MD, -2.62; 95% CI, -5.29 to 0.04; NS). Low certainty evidence supported duloxetine (MD, -2.7; 95% CI, -5.03 to -0.37) and vortioxetine (MD, 0.6; 95% CI, -2.52 to 3.72; NS), while very low certainty evidence supported other antidepressants evaluated and placebo. Suicide-related outcomes were generally low and resulted in wide confidence intervals and generally low or very low certainty of results. Notably, not all agents evaluated carry FDA-approval in the included age range evaluated.

A systematic review and meta-analysis assessed the optimal dose of SSRIs (excluding fluvoxamine), venlafaxine, and mirtazapine in the acute treatment of adults with MDD (77 studies; n=19,364).<sup>278</sup> Doses of SSRIs were assessed in fluoxetine equivalents. The authors assessed treatment response ( $\geq 50\%$  reduction in target symptoms), dropouts secondary to adverse effects, and all-cause dropouts after a median of 8 weeks of treatment. For the SSRIs, there was a dose response at all doses; however, there was a gradual increase from 20 mg to 40 mg fluoxetine equivalents followed by flat to decreasing trends at higher approved fluoxetine equivalent doses. Venlafaxine was found to have an increasing dose-efficacy relationship up to doses of 150 mg, followed by a slower increase in dose-efficacy at higher doses. Mirtazapine was found to have dose-efficacy response up to 30 mg, followed by a decrease in dose-efficacy response at higher doses. There was a dose-dependent increase in dropouts for all medications due to adverse events.

## Generalized Anxiety Disorder

A systematic review and network meta-analysis of 89 studies (n=24,441) assessed the effects of antidepressants for the treatment of GAD.<sup>279</sup> Among the SSRIs, escitalopram (-2.45; 95% CI, -3.27 to -1.63), citalopram (-2.22; 95% CI, -4.29 to -0.19), fluoxetine (-2.43; 95% CI, -3.74 to -1.16), and sertraline (-2.88; 95% CI, -4.17 to -1.59) were all found to be effective and tolerable when compared to placebo in mean change in HAM-A from baseline; however, data with citalopram, fluoxetine, and sertraline were limited by sample sizes. Paroxetine was found to be efficacious but was limited by tolerability compared to placebo (odds ratio favoring placebo, 1.24; 95% CI, 1.03 to 1.5). Notably, several included trials were not completed in the US; however, this is the largest, most recent network meta-analysis of these agents for GAD.

## Panic Disorder

A network meta-analysis of 87 studies assessed the efficacy of 12 classes of drugs, including SSRIs and other antidepressants, for the treatment of adults with panic disorder with or without agoraphobia (n=12,800).<sup>280</sup> The authors evaluated the agents by remission rate, dropouts, anxiety scores, depression



scores, and adverse effects. Notably, the evaluations focused on the class of agents; thus, differences between SSRIs were limited. Upon an evaluation of only SSRIs, fluoxetine, fluvoxamine, paroxetine, and sertraline were all found to be more efficacious than placebo for achieving remission. Using a surface under cumulative ranking curves (SUCRA) cluster ranking plot, the authors determined that sertraline and escitalopram were the most efficacious agents with the lowest risk of adverse events, while fluvoxamine, paroxetine, and fluoxetine had favorable efficacy but a higher risk of adverse events. Notably, citalopram showed minimal efficacy in remission and had a high risk of adverse events. Due to the limited SSRI-specific data, results should be interpreted cautiously.

## Premenstrual Dysphoric Disorder

A systematic review of 31 randomized, controlled trials evaluating treatment of premenstrual syndrome (PMS) with SSRIs was recently published.<sup>281</sup> Studies enrolled women with a prospective diagnosis of PMS, PMDD, or late luteal phase dysphoric disorder and compared fluoxetine, paroxetine, sertraline, escitalopram and citalopram with placebo. The overall quality of evidence was rated as low to moderate with the primary weakness being poor reporting of methods. Treatment with an SSRI significantly reduced overall self-rated symptoms compared to placebo but the effect size was small in pooled analysis of trials reporting change scores. Evidence comparing administration during luteal phase versus continuous regimens showed no clear difference, but there were very few trials directly comparing these regimens. Discontinuation due to adverse events was more frequent in the SSRI groups compared to placebo groups; the most common adverse events were nausea and asthenia.

## Social Anxiety Disorder

A network meta-analysis of 45 studies assessed the effects of antidepressants, as well as other medications, for the treatment of social anxiety disorder.<sup>282</sup> The assessment included the following antidepressants: atomoxetine, escitalopram, fluvoxamine, paroxetine, sertraline, mirtazapine, phenelzine, venlafaxine, and vilazodone. Only paroxetine was found to differ from placebo significantly in improvement in symptom severity (MD, -15.89 [95% CI, -29.94 to -1.84]) based on data from trials of all pharmacologic treatments included in the analysis; however, the authors cautioned that this was based on low to very low quality evidence. Regarding dropout rate, no statistically significant difference was found, although this was based on low to very low quality evidence as well.

## SUMMARY

SSRIs are generally considered first-line therapy for their FDA-approved indications. There is no significant evidence that any other class of drugs is more effective than SSRIs. Despite the differences in pharmacokinetic actions of each agent, the full response time for all SSRIs takes typically 4 to 6 weeks. A clinician should allow 4 to 6 weeks to determine responsiveness to a SSRI in a patient prior to trying another agent in the SSRI class. Similarly, the SSRI agents approved for use in generalized anxiety disorder, social anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder, and premenstrual dysphoric disorder have comparable efficacy and adverse event profiles. SSRIs are the recommended first-line medications for the treatment of post-traumatic stress disorder. These drugs decrease the 3 symptom domains of concern in this syndrome: re-experiencing, avoidance/numbing, and hyperarousal.

Paroxetine mesylate (Brisdelle), a 7.5 mg paroxetine mesylate capsule, is the only SSRI currently approved for vasomotor symptoms associated with menopause. Brisdelle is not indicated for the treatment of any psychiatric condition.

Four of the products are approved for pediatric use: escitalopram, fluoxetine, fluvoxamine, and sertraline. Fluoxetine and escitalopram are FDA-approved for treatment of depression in children. Fluoxetine, sertraline, and fluvoxamine are approved for treatment of obsessive-compulsive disorder in children. The FDA approved revised labeling for all antidepressant drugs with a boxed warning and expanded warning statements alerting healthcare providers to an increased risk of suicidality (suicidal thinking and behavior) in children, adolescents, and young adults being treated with these agents.

These agents have similar adverse event profiles with gastrointestinal disturbances (constipation, diarrhea, nausea), central nervous system effects (dizziness, headache, insomnia, somnolence), and sexual adverse events being most commonly reported; however, there are differences among SSRIs in the incidence of other adverse events. Paroxetine tends to cause weight gain while fluoxetine tends to cause weight loss. Paroxetine also has the highest rate of sexual adverse events.

If stopped abruptly, all SSRIs can cause discontinuation symptoms, such as agitation, anxiety, confusion, headache, insomnia, sweating, vomiting, and tremor. Fluoxetine, with the longest half-life (2 to 7 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, may have a quicker onset of action but also has a higher rate of discontinuation symptoms.

The SSRIs differ markedly in their potential to cause interactions with other drugs. Because of substantial inhibition of one or more cytochrome P450 enzymes at therapeutic doses, fluoxetine, fluvoxamine, fluvoxamine CR, and paroxetine 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. The drug interaction profiles with the fewest interactions belong to citalopram and escitalopram, followed by sertraline. Escitalopram is an isomer of citalopram.

All SSRIs carry a class warning for serotonin syndrome which has been reported when these agents are taken by themselves or with other serotonergic agents such as triptans, tramadol, amphetamines, linezolid, lithium, and SNRIs. If symptoms of serotonin syndrome such as hyperthermia, agitation, and incoordination develop, the SSRI must be discontinued immediately and supportive treatment initiated.

Fluoxetine is a relatively energizing SSRI; therefore, it may increase alertness, cause mild jitteriness, and insomnia. As a result, it is best taken in the morning and may be preferable for lethargic depression. Paroxetine, on the other hand, is more sedating and constipating, most likely due to its antihistamine and anticholinergic activity, respectively. Sertraline is neither activating nor sedating, but it may cause loose stool.

All the SSRIs are associated with an increased risk of complications toward the neonate if taken during pregnancy, but paroxetine especially has been associated with an increased risk of cardiac malformations if taken during the first trimester. Both the FDA and American College of Obstetricians and Gynecologists (ACOG) recommend thorough consideration of the risks versus the benefits to both the woman and the neonate if SSRI treatment is to continue through pregnancy.

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