

IOWA MEDICAID P & T COMMITTEE

THERAPEUTIC CLASS REVIEW

NOVEMBER 13, 2008

ANTIDEPRESSANTS, SSRIS

SYNOPSIS

A depressive disorder is an illness that hinders normal functioning and impedes daily life, in addition to causing pain to the person with the disorder as well as the people in their lives. There are many forms of depressive disorders, but the most common form is major depressive disorder or MDD.⁴² The prevalence of MDD in children is approximately 2%, but increases to 4-8% in adolescents. According to community samples, the incidence rises to about 20% by the age of 18.⁴⁰ Several studies with adults and children advocate that each successive generation since 1940 are at a higher risk of developing a depressive disorder, with the onset occurring at an earlier age.⁴⁰ Most who experience a depressive disorder do require treatment.⁴²

Depressive disorders, such as MDD are often accompanied with other medical conditions, including psychiatric conditions.⁴² Although dependent on the setting and source of referral, it was found that that 40% to 90% of youths with depressive disorder also have a co-morbid psychiatric disorder.⁴⁰ Anxiety disorder was labeled as being the most prominent co-morbid diagnosis with MDD. With that said, many of the newer antidepressants do have co-existing indications for anxiety disorder.⁴²

An antidepressant is defined as a psychiatric medication used for improving, preventing or treating major depression. Up until the 1950's, opiates were used as an antidepressant; however, due to tolerance and dependence issues, as well as side effects, their use faded for this condition. During the 1950's and 1960's, development of newer compounds for treatment occurred, including tri-cyclic compounds and MAOIs. Eventually it was hypothesized that one cause of depression may be from a decrease in a chemical in the brain called serotonin, which is used to transmit signals between neurons.⁴³ It wasn't until 1988 that the first Selective Serotonin Reuptake Inhibitor (SSRI) fluoxetine was approved for use. With this development, other SSRIs were introduced. SSRI thus use became the most popular form of treatment.⁴¹ In the United States, antidepressant use has doubled between the years of 1995 and 2002.⁴¹ In addition, reports show that in 2006, the SSRI Zoloft was the most prescribed antidepressant in the United States.⁴⁰

Antidepressants, SSRIs-2

The drugs included in this therapeutic class review include: citalopram (Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®, Rapiflux®, Sarafem®), fluvoxamine (tabs and Luvox® CR caps), paroxetine (Paxil®, Paxil CR®, Pexeva®), and sertraline (Zoloft®).

FDA APPROVED INDICATIONS¹⁻⁹

All FDA approved indications listed in the table below for the SSRI class are for adults. For children, Zoloft® carries an FDA approved indication of obsessive-compulsive disorder (OCD) in ages 6-17. Fluvoxamine and fluoxetine are both indicated for use in OCD in children ages 8-17. In addition, fluoxetine not only has several studies supporting its efficacy for MDD in youth, aged 8-18, but it also has FDA approval for use in depression in this population. There are individual double-blind placebo-controlled (DBCP) studies that support the use of Zoloft® and Celexa® for use in MDD (see Special Populations), but no FDA approval.^{20,21} There has most recently been a new extended-release formulation of fluvoxamine approved for use, called Luvox® CR.

Drug	Major Depressive Disorder (MDD)	Obsessive Compulsive Disorder (OCD)	Panic Disorder	General Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Post Traumatic Stress Disorder (PTSD)	Bulimia Nervosa	Pre-menstrual Dysphoric Disorder (PMDD)
citalopram (Celexa®)	X							
escitalopram (Lexapro®)	X			X				
fluoxetine (Prozac®)	X	X	X				X	
fluoxetine (Sarafem®)								X
fluvoxamine		X						
fluvoxamine (Luvox® CR)		X			X			
paroxetine hydrochloride (Paxil®)	X	X	X	X	X	X		
paroxetine hydrochloride (Paxil CR®)	X		X		X			X

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Drug	Major Depressive Disorder (MDD)	Obsessive Compulsive Disorder (OCD)	Panic Disorder	General Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Post Traumatic Stress Disorder (PTSD)	Bulimia Nervosa	Pre-menstrual Dysphoric Disorder (PMDD)
paroxetine Mesylate (Pexeva®)	X	X	X	X				
sertraline (Zoloft®)	X	X	X		X	X		X

DOSAGE FORMS, DOSE, MANUFACTURER¹⁻⁹

Luvox® has been discontinued by the manufacturer, but the generic is still available.

Drug	Dosage Forms	Dose	Manufacturer
citalopram (Celexa®)	<u>Tablets:</u> 10mg, 20mg, 40mg <u>Oral Solution:</u> 10mg/5ml	20-40mg daily	Various generic manufacturers (Forest Laboratories Inc.)
escitalopram (Lexapro®)	<u>Tablets:</u> 5mg, 10mg, 20mg <u>Oral Solution:</u> 5mg/5ml	10-20mg daily	Forest Laboratories Inc.
fluoxetine (Prozac®) (Sarafem®)	<u>Prozac Pulvules:</u> 10mg, 20mg, 40mg <u>Oral Solution:</u> 20mg/5ml <u>Prozac Weekly Capsules:</u> 90mg <u>Sarafem Capsules:</u> 10mg, 20mg	<u>Pulvules/Solution:</u> <u>Adults:</u> 20-80mg daily <u>Children:</u> 10-60mg daily <u>Prozac Weekly:</u> 90mg once weekly <u>Sarafem:</u> 20mg daily or intermittently (day 14 of cycle → 1 st day of menses), max 60mg	Various generic manufacturers (Eli Lilly and Company) (OSG Norwich Pharmaceuticals, Inc)
fluvoxamine (Luvox®) (Luvox® CR)	<u>Tablets:</u> 25mg, 50mg, 100mg <u>Extended-Release Caps:</u> 100mg, 150mg	<u>Adults (tabs/caps):</u> 100-300mg daily <u>Children 8-17 (tabs only):</u> 50-200mg daily. <i>Max daily dose for 8-11 years: 200mg</i>	Various generic manufacturers (Jazz Pharmaceuticals)

Drug	Dosage Forms	Dose	Manufacturer
		<i>Max daily dose ≥ 12: 300mg.</i>	
paroxetine HCl (Paxil®) (Paxil CR®)	<u>Tablets:</u> 10mg, 20mg, 30mg, 40mg <u>Oral Suspension:</u> 10mg/5ml <u>Controlled-Release Tabs:</u> 12.5mg, 25mg, 37.5mg	<u>Tablets/Oral Suspension:</u> 20-60mg daily <u>CR Tablets:</u> 25mg-62.5mg once daily	Various generic manufacturers (GlaxoSmithKline)
paroxetine mesyl. (Pexeva®)	<u>Tablets:</u> 10mg, 20mg, 30mg, 40mg	10-60mg daily	JDS Pharmaceuticals
sertraline (Zoloft®)	<u>Tablets:</u> 25mg, 50mg, 100mg <u>Oral Solution (12% alcohol):</u> 20mg/ml	25-200mg once daily	Various generic manufacturers (Pfizer)

PHARMACOLOGY¹⁻⁹

The mechanism of action for all the medications in this class of Selective Serotonin Reuptake Inhibitors (SSRIs) is the same. This whole class potentiates serotonergic activity by inhibiting the central nervous system (CNS) neuronal uptake of serotonin (5HT). These medications are highly selective for serotonin receptors in contrast to tricyclic antidepressants (hence the name SSRIs), and they have varying and unique affinities for norepinephrine, dopamine, and antagonisms for muscarinic, histaminergic and α_1 -adrenergic receptors which are responsible for their individual adverse drug reaction (ADR) profiles.

PHARMACOKINETICS¹⁻⁹

Except for fluoxetine, the half-life of the rest of the SSRIs varies from 15 to 35 hours. As a result, fluvoxamine IR must be given at least twice daily and the rest, once daily. Fluoxetine has an active metabolite, norfluoxetine, which has a half-life of up to 2 weeks, and as a result, although it is usually administered daily, it can be given every other day or even every third day and steady state can be maintained once it is reached. Conversely, if fluoxetine is discontinued, it may take up to several weeks before it is completely out of the blood stream. Even though the time to steady state for the once daily and once weekly fluoxetine are the same, the concentrations are approximately 50% lower for the once weekly formulation vs the once

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daily formulation. The Prozac weekly formulation containing 90 mg of fluoxetine equals 7 days of 20mg of once-a-day fluoxetine. The fluoxetine capsule, solution, and once weekly delayed-release capsule are bioequivalent as is the paroxetine HCL tablet and suspension. Paroxetine CR tablets include a degradable polymeric matrix called a GEOMATRIX™, which allows for a slow dissolution of 4-5 hours, and the tablets have an enteric coating which impedes the initiation of release until after it's moved out of the stomach. The controlled release formulations of SSRIs have lower CMax compared to the immediate release formulations and smaller fluctuations between peak and trough drug concentrations, which may improve the tolerability of these agents in some individuals. Pharmacokinetic studies of the SSRIs in youth are quite limited but generally support lower dosing or more frequent dosing.

Drug	Time to Steady State/ Peak Plasma Concentration	Half-Life	Elimination	Other
citalopram (Celexa®)	One week 4 hrs (peak plasma)	35 hours	Urine: 20%	
escitalopram (Lexapro®)	One week 5 hrs (peak plasma)	27-32 hours	Urine: 7%	
fluoxetine (Prozac®) (Sarafem®) (Prozac Weekly®)	4-5 weeks 6-8 hrs (peak plasma)	4-6 days	Hepatic	t _{1/2} of active metabolite- 4-16 days
fluvoxamine	One week 3-8 hrs (peak plasma)	15 hrs	Urine: 94%	
fluvoxamine (Luvox® CR)	One week	16.3 hrs	Urine: 94% Feces: 2%	
paroxetine HCl (Paxil®)	10 days 5.2 hrs (peak plasma)	21 hrs	Urine: 64% Feces: 36%	
paroxetine mesylate (Pexeva®)	13 days	33.2 hrs	Urine: 64% Feces: 36%	
paroxetine CR (Paxil® CR)	2 weeks 6-10 hrs (peak plasma)	15-20 hrs	Urine: 64% Feces: 36%	
sertraline (Zoloft®)	One week 4.5-8.4 hrs (peak plasma)	26 hours	Urine: 40-50% Feces: 40-50%	t _{1/2} of active metabolite- 62-104 hrs

CLINICAL TRIALS

Despite their differing FDA-approved indications, when comparable dosages are used, in most meta-analyses, individual SSRIs in comparison to each other have been found to be equally effective but may vary

Antidepressants, SSRIs-6

in side effect profiles in treating depressive and anxiety disorders and premenstrual dysphoric disorder in adults.^{14,15,17,18,19,22,23,24,}

There is a FDA black box warning describing a small increased risk for all antidepressants of increased suicidality in youth and young adults from 18-24 years. For childhood depression only fluoxetine has FDA approval, and there are several DBPC trials that support its efficacy in MDD and in preventing relapse.^{26,27} For childhood OCD, a meta-analysis of trials with paroxetine, fluoxetine, fluvoxamine and Zoloft® has shown them to be equally effective.¹⁶

CONTRAINDICATIONS¹⁻⁹

All medications in this therapeutic class carry a contraindication of hypersensitivity to their active ingredient or to any component of the compound. All carry a contraindication of concurrent use of pimozide because increases in its concentration due to CYP3A4 inhibition by the SSRIs can lead to prolongation of QTc interval. In addition, concurrent use or use within 14 days of MAOIs (including Zyvox) is contraindicated.

There are several drugs in particular that carry their own contraindications unique to the class. These contraindications are listed in the table below.

Drug	Contraindication
fluoxetine (Prozac®) (Sarafem®) (Prozac Weekly®)	Thioridazine should not be used concurrently or within 5 weeks of discontinuation of fluoxetine.
fluvoxamine	Thioridazine, tizanidine, mesoridazine, or cisapride
fluvoxamine (Luvox® CR)	Alosetron, tizanidine, thioridazine
paroxetine (Paxil® tabs/CR) (Pexeva®)	Thioridazine
sertraline (Zoloft® Soln.)	Concomitant use of the oral concentration with antabuse, due to alcohol content in oral concentration.

SPECIAL POPULATIONS¹⁻⁹

Along with all antidepressants, all SSRIs share a black box warning discussing the risk of increased suicidality in youth less than 18 years of age. Starting in June 2003, the FDA issued a “talk paper” in which paroxetine

was singled out for increased suicidal risk. This increased risk was confirmed by the FDA’s review of all antidepressant studies in youth submitted to it and reviewed by Columbia, using their newly developed criteria. The data is reviewed by Bridge et al 2005 who compared the number need to treat (NNT) vs. the number need to harm (NNH) from antidepressant studies in youth and found positive results for fluoxetine, Zoloft®, and Celexa® and negative ones for paroxetine (and venlafaxine).³¹ In October 2004, the FDA issued its warnings on suicidality for all antidepressants in youth and recommended careful monitoring with antidepressant initiation, as well as with increases and decreases in dosing. In the table below, the pediatric column indicates whether the safety and efficacy have been established in children under the age of 18.

(<http://www.fda.gov/CDER/Drug/antidepressants/SSRIPHA200410.htm>)

Drug	Pediatrics	Pregnancy Category	Dosage change with Renal Insufficiency	Dosage change with Hepatic Insufficiency
citalopram (Celexa®)	No	C	Mild to moderate: Not required Severe: Not studied.	t½ doubled and clearance ↓, so initiate dose at 20mg
escitalopram (Lexapro®)	No	C	Mild to moderate: Not required Severe: Not studied.	T½ doubled and clearance ↓, so initiate dose at 10mg
fluoxetine (Prozac®) (Sarafem®)	≥ 8 in MDD and OCD	C	Not required	Use with caution: initiate with a ↓ dose or ↓ dosing frequency
fluvoxamine	≥ 8 in OCD	C	Use with caution: ↓ dose	Use with caution: ↓ dose
fluvoxamine (Luvox® CR)	No	C	Not required	Not required
paroxetine (Paxil® tabs/CR) (Pexeva®)	No	D	Initial dose should be ↓	Initial dose should be ↓
sertraline (Zoloft®)	≥6 in OCD	C	Not required	Mild to Moderate: ↓ dose or ↓ dosing frequency Severe: Not studied

OCD- Obsessive Compulsive Disorder

ADVERSE DRUG REACTIONS³⁸

The tables below list the adverse drug reactions (ADRs) that were a cause for discontinuation of therapy expressed as a percentage of total number for adults.³⁸ Somnolence, insomnia and nausea were the most common ADRs that led to discontinuation of treatment. The percentages of each individual ADR varied greatly between medications. For example, headache and somnolence was most common with Luvox® CR, diarrhea with Zoloft®, and nervousness with fluoxetine.

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Cardiovascular Side Effects ³⁸	CTP	ECTP	FXT	FVX	FVX CR	PXT IR	PXT CR	SRT
Chest pain	-	≥ 1	≥1	-	0-3	3	1	≥ 1
Hypertension	0.1-1	≥ 1	≥ 1	≥ 1	0-2	≥ 1	2	0.1-1
Hypotension (postural)	≥ 1	-	0.1-1	≥ 1	-	-	0.1-1	0.1-1
Palpitations	-	≥ 1	1-3	3	0-3	2-3	0.1-1	≥ 1
Vasodilation	-	-	2-3	3	0-2	2-4	2-3	< 0.1

(CTP-Citalopram, ECTP-Escitalopram, FXT-Fluoxetine, FVX-Fluvoxamine, PXT-Paroxetine, SRT-Sertraline)

CNS Side Effects ³⁸	CTP	ECTP	FXT	FVX	FVX CR	PXT IR	PXT CR	SRT
Abnormal dreams	-	3	3	-	0-3	3-4	1	0.1-1
Agitation	3	0.1-1	≥ 1	2	2-3	3-6	2-3	1-6
Anxiety	4	-	12-13	1-5	6-8	2-6	2-5	4
Concentration impaired	≥ 1	≥ 1	-	-	-	3-4	1-3	-
Dizziness	-	4-7	2-11	2-11	12-15	6-14	6-14	6-17
Fatigue	5	2-8	-	-	-	-	-	10-16
Headache	-	24	13-24	3-22	32-35	17-18	15-27	25
Insomnia	15	7-14	9-24	4-21	32-35	11-24	7-20	12-28
Libido decreased	1-4	3-7	3-9	2	6	3-12	7-12	1-11
Nervousness	-	0.1-1	3-14	2-12	0-10	3-9	2-8	5
Paresthesia	≥ 1	2	-	-	0-3	4	1-3	2
Somnolence	18	4-13	12-13	4-22	26-27	13-24	3-22	2-15
Tremor	8	0.1-1	9-12	5	6-8	4-15	4-8	< 1-11

(CTP-Citalopram, ECTP-Escitalopram, FXT-Fluoxetine, FVX-Fluvoxamine, PXT-Paroxetine, SRT-Sertraline)

Dermatologic Side Effects ³⁸	CTP	ECTP	FXT	FVX	FVX CR	PXT IR	PXT CR	SRT
Pruritus	≥ 1	0.1-1	3	-	-	≥ 1	0.1-1	0.1-1
Rash	≥ 1	≥ 1	4-5	-	-	2-3	≥ 1	3
Sweating, increased/excessive	11	3-8	7-8	7	6-7	1-14	6-14	3-11

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(CTP-Citalopram, ECTP-Escitalopram, FXT-Fluoxetine, FVX-Fluvoxamine, PXT-Paroxetine, SRT-Sertraline)

GI Side Effects ³⁸	CTP	ECTP	FXT	FVX	FVX CR	PXT IR	PXT CR	SRT
Abdominal Pain	3	2	6	1	-	4	3-7	2-7
Anorexia	4	-	10-11	1-6	13-14	-	-	3-11
Constipation	-	3-6	5	10	4-6	5-16	2-13	1-8
Decreased appetite	-	3	-	-	-	2-9	1-12	-
Diarrhea/loose stools	8	6-14	2-11	1-11	14-18	9-19	6-18	13-24
Dry mouth	20	4-9	9-11	1-14	-	9-21	2-18	6-16
Dyspepsia	5	2-6	7-8	1-10	8-10	2-5	2-13	6-13
Flatulence	≥ 1	2	3	4	-	4	6-8	-
Nausea	21	15-18	9-27	9-40	34-39	15-36	17-23	13-30
Vomiting	4	3	1-3	2-5	0-6	2-3	2	4

(CTP-Citalopram, ECTP-Escitalopram, FXT-Fluoxetine, FVX-Fluvoxamine, PXT-Paroxetine, SRT-Sertraline)

GU Side Effects ³⁸	CTP	ECTP	FXT	FVX	FVX CR	PXT IR	PXT CR	SRT
Abnormal ejaculation	6	9-14	-	8	10-11	6-28	15-27	7-19
Female genital disorders	-	-	-	-	-	2-9	2-10	-
Male genital disorders, other	-	-	-	-	-	4-10	-	-
Sexual Dysfunction	1-3	2-6	0.1-1	2	2-4	2-13	5-10	≥ 1
Urinary frequency	-	≥ 1	2	3	-	2-3	2	0.1-1
Urination disorder/retention	0.1-1	-	0.1-1	1	-	3	2	0.1-1

(CTP-Citalopram, ECTP-Escitalopram, FXT-Fluoxetine, FVX-Fluvoxamine, PXT-Paroxetine, SRT-Sertraline)

Respiratory Side Effects ³⁸	CTP	ECTP	FXT	FVX	FVX CR	PXT IR	PXT CR	SRT
Cough (increased)	≥ 1	≥ 1	-	≥ 1	-	≥ 1	1-2	0.1-1
Pharyngitis	-	-	6-10	-	0-6	4	8	-
Rhinitis	5	5	16-23	-	-	3	4	≥ 1

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Respiratory Side Effects ³⁸	CTP	ECTP	FXT	FVX	FVX CR	PXT IR	PXT CR	SRT
Sinusitis	3	3	-	≥ 1	-	4	4-8	0.1-1
Yawn	2	2	3-5	2	2-5	2-5	2-5	≥ 1

(CTP-Citalopram, ECTP-Escitalopram, FXT-Fluoxetine, FVX-Fluvoxamine, PXT-Paroxetine, SRT-Sertraline)

Miscellaneous Side Effects ³⁸	CTP	ECTP	FXT	FVX	FVX CR	PXT IR	PXT CR	SRT
Asthenia	-	0.1-1	8-14	2-14	24-26	3-22	14-18	≥ 1
Fever	2	≥ 1	2-5	-	-	-	0.1-1	0.1-1
Flu syndrome	0.1-1	5	3-12	3	-	5-6	6-8	-
Myalgia	2	≥ 1	-	-	0-5	2-4	5	≥ 1
Pain	-	-	3-9	-	0-10	-	3	1-6
Weight gain	≥ 1	≥ 1	≥ 1	≥ 1	-	≥ 1	1-3	≥ 1
Weight loss	≥ 1	0.1-1	2-3	≥ 1	0-2	0.1-1	1	0.1-1

(CTP-Citalopram, ECTP-Escitalopram, FXT-Fluoxetine, FVX-Fluvoxamine, PXT-Paroxetine, SRT-Sertraline)

Although not listed in the above tables as an ADR, all SSRIs reduce platelet serotonin and may be associated with some individuals experiencing GI bleeding especially when combined with aspirin or NSAIDs.^{32,33}

Children appear to have an increased and unique ADR profile as compared to teens or adults. Because of the possibility of changes in weight or growth, the FDA has recommended clinical monitoring of height and weight. Different studies use different terms to describe ADRs, but a comparable study to the one for adults whose table are shown was completed for children, adolescents and adults by Safer and Zito (2006). It revealed that nervousness (which they termed akathisia) and vomiting that led to a discontinuation of treatment of all SSRIs were 2-3 times more common in children than in teens and uncommon in adults, and conversely children and teens experience less somnolence overall than adults. There is insufficient data to compare the ADRs of individual SSRIs in youth. Fluoxetine has the most data. In the Treatment for Adolescents with Depression study (TADS), only 2% of subjects who received fluoxetine experienced significant ADRs of sedation, insomnia, vomiting and abdominal pain.³⁵

An uncommon but significant ADR for all antidepressants is the induction of mania in adults with unipolar depression or bipolar depression (BD). In the former group, approximately 1% of adults have a manic-shift with all antidepressants.³⁶ In the latter, SSRIs may be responsible for a 4% manic induction rate in those without mood stabilizers as compared to 11% with tricyclic antidepressants.³⁶ There is insufficient data to suggest any differences between individual SSRIs. More recent studies confirm the increased risk of manic inductions in individuals with BD with tricyclic usage in those without mood stabilizers.³⁷ The only large-scale

systematic but administrative study of manic induction in youth on antidepressants suggests that there is about a 5% induction rate for youth without previous history of mania with tricyclics showing the highest hazard rate of 3.9 vs 2.1 for SSRIs. The highest rates occurred in the 10-to-14 year old group.³⁹

DRUG-DRUG INTERACTIONS¹⁻⁹

Celexa®:

Celexa® is primarily metabolized by CYP3A4 and CYP2C19; however, co-administration of a potent CYP3A4 inhibitor, ketoconazole, or a potent CYP3A4 inducer, carbamazepine showed no significant pharmacokinetic effect on Celexa®. The addition of a potent CYP2C19 inhibitor such as fluvoxamine will significantly increase Celexa® concentration, the s-enantiomer more than the R-enantiomer. Celexa® is a modest CYP2D6 inhibitor, and it will increase the concentration of CYP2D6 substrates such as desipramine, nortriptyline and others. Most of the drug interactions described in the product insert is pharmacodynamics.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
warfarin	Unknown, may be pharmacodynamic	Due to 5% ↑ in Prothrombin time, PT must be monitored
MAOIs	Additive pro-serotonergic	Combination is contraindicated. Wait at least 14 days prior to starting MAOI once d/c Celexa®
alcohol	Additive side effects	Combination not recommended
5-HT1 Receptor Agonists (e.g., Sumatriptan)	Additive pro-serotonergic	↑d risk of serotonin syndrome
other CNS drugs	Additive side effects	Use with caution
tramadol	Additive pro-serotonergic	↑ risk of serotonin syndrome
linezolid (Zyvox®)	Additive pro-serotonergic	↑ risk of serotonin syndrome. Use contraindicated.
St. John's Wart	Additive side effects	Avoid combination due to increase sedative-hypnotics effect

Lexapro®:

Lexapro® is metabolized primarily by CYP2C19, but CYP3A4 and CYP2D6 are minor contributors. Ritonavir, a potent CYP3A4 inhibitor has no effect on the pharmacokinetics of Lexapro®. Omeprazole, a potent CYP2C19 inhibitor can increase AUC of Lexapro® by 50% but because of its wide therapeutic index, this is of little clinical consequence. Lexapro® is a modest CYP2D6 inhibitor. The DDIs listed in the product insert are mostly pharmacodynamic.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
warfarin	Unknown, may be pharmacodynamic	Due to 5% ↑ in Prothrombin time, PT must be monitored
MAOIs	Additive pro-serotonergic	Combination is contraindicated. Wait at least 14 days prior to starting MAOI once d/c Lexapro®
alcohol	Additive side effects	Combination not recommended
linezolid (Zyvox®)	Additive pro-serotonergic	↑ risk of serotonin syndrome. Use contraindicated.
other CNS drugs	Additive side effects	Use with caution
drugs that interfere with Hemostasis (NSAIDs, ASA, Warfarin)	Pharmacodynamic	Use with caution and monitor since Lexapro® may ↑ bleeding effects of these drugs.
CYP2C19 inhibitors/Inducers		Use with caution and monitor

Fluoxetine:

This drug utilizes CYP2C9, 3A4 and 2D6 pathways and minor routes, CYP2B6 and 2C19, and because of the multiplicity of pathways, it is relatively invulnerable to other CYP inhibitors or inducers. It is a potent inhibitor of CYP2D6 and modestly inhibits most of the other P450 cytochromes, and as a result, it increases the concentration of CYP2D6 (e.g., nortriptyline, desipramine, dextromethorphan, metoprolol, perphenazine and many others). Drugs like olanzapine which utilize CYP2D6 as a minor pathway can have concentrations increased up to 15-30%. Since norfluoxetine is a moderate inhibitor of CYP3A4 and fluoxetine, a modest inhibitor of CYP2C8, concentrations of carbamazepine, a substrate of CYP3A4 and CYP2C8 will increase. Over time, carbamazepine will induce some of the CYP pathways of fluoxetine and concentration of fluoxetine will decrease. Combination use of fluoxetine with other pro-serotonergic drugs may cause increased risk of serotonin syndrome.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
warfarin	CYP2C9 inhibition and CYP3A4 inhibition with s-warfarin substrate of CYP2C9 and R-warfarin substrate of CYP3A4. Also may be pharmacodynamic.	Monitor Prothrombin Time (PT) since increased bleeding may occur
olanzapine	CYP2D6 inhibition with olanzapine substrate of CYP2D6	May need to slightly ↓ dose of olanzapine
linezolid (Zyvox®)	Additive pro-serotonergic	↑ risk of serotonin syndrome. Use contraindicated.
other CNS drugs	Additive side effects	Use with caution
St. John's Wort	Additive side effects	Avoid combination due to increase sedation
MAOIs	Additive pro-serotonergic	Combination is contraindicated. Wait 14 days prior to

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
		starting MAOI once d/c fluoxetine
carbamazepine	CYP3A4/CYP2C19	↑ of Carb and ↓ of fluoxetine; Monitor
benzodiazepines	CYP3A4/CYP2C19	Diazepam t½ is ↑ and ↑ levels of alprazolam

Fluvoxamine:

Fluvoxamine is a substrate of CYPs 1A2 and 2D6 and is vulnerable to CYP inhibition or induction at those sites (smoking will reduce Fluvoxamine levels by 66%). Fluvoxamine is a pan-inhibitor (CYP1A2, 2B6, 2C9, 2C19 and 3A4; a potent inhibitor of CYP1A2 and 2C19). As a result, drugs that are substrates of either CYP1A2 or 2C19 or both can be affected. Melatonin AUC increases 3-fold and Ramelteon 70-fold via CYP1A2 inhibition (with the latter combination contraindicated) and a 4-fold increase in lansoprazole via CYP2C19.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
warfarin	CYP2C9, 2C19 and 3A4 inhibition affecting both S and R-warfarin. Also may be pharmacodynamic.	Monitor PT and adjust if necessary
MAOIs	Pro-serotonergic	Combination is contraindicated. Wait at least 14 days prior to starting MAOI once d/c fluvoxamine
TCA's	CYP2D6 inhibition of primary TCAs and CYP1A2, 2C9, 2C19 and 3A4 of secondary TCAs	Monitor and adjust dose if necessary
clozapine	CYP1A2 inhibition	Use combination w/caution. Monitor and adjust dose.

Paroxetine HCL and Paroxetine Mesylate:

Paroxetine is both a substrate and a potent inhibitor of CYP2D6. Levels of drugs that are entirely or principally metabolized by CYP2D6 and additionally, those that have a narrow therapeutic index are most at risk from CYP2D6 inhibition by paroxetine for serious DDIs (e.g., desipramine, nortriptyline, type 1C antiarrhythmics: flecainide, encainide).

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
warfarin	May be pharmacodynamic.	Monitor Prothrombin Time (PT) since ↑ bleeding may occur
TCA's	CYP2D6	Monitor and adjust dose if necessary
atomoxetine	CYP2D6	↓ Strattera® dose
risperidone	CYP2D6	Risperdal levels ↑ and should ↓ dose

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
MAOIs	Pro-serotonergic	Combination is contraindicated. Wait at least 14 days prior to starting MAOI once d/c paroxetine

Zoloft®:

Zoloft® is metabolized by at least 5 P450 cytochromes (e.g., CYP3A4, 2C9, 2C19, 2B6, 2D6) and several UGTs and is therefore relatively invulnerable to drug interactions via P45 cytochrome inhibition or induction unless the drug is a pan-inhibitor or pan-inducer. It is a mild inhibitor of CYP2D6 unless it is given at its highest dosage when it becomes a moderate CYP2D6 inhibitor (e.g., at less than 100 mg of Zoloft®, desipramine is increased only 25-40%). Most of the DDI listed in the product insert are pharmacodynamic.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
warfarin	Mechanism unknown, may also be through pharmacodynamic mechanisms	Due to 8% ↑ in Prothrombin time (during and up to 21 days after Zoloft® is d/c), PT must be monitored
MAOIs	Pro-serotonergic	Combination is contraindicated. Wait at least 14 days prior to starting MAOI once d/c Zoloft®
alcohol	Additive side effects	Combination not recommended
St. John's wort	Additive side-effects	Avoid combination due to increase sedative-hypnotics effect
5-HT1 Receptor Agonists	Pro-serotonergic	Increased risk of serotonin syndrome

SUMMARY

Although there are variations in FDA-approval of SSRIs for various anxiety disorders and for major depression in adults, meta-analyses have shown that no SSRI is superior to another in terms of efficacy. However, there are pharmacokinetic differences between the SSRIs. Fluoxetine should be considered a 'depot form' of an SSRI- having a prolonged 2 week or more half-life because of its long-lived active metabolite norfluoxetine. The other SSRIs have a 24-hour half-life except for fluvoxamine which has a 12-hour half-life.

For children, although there are only 3 SSRIs with FDA-approval for anxiety disorders, all the SSRIs can be utilized. For major depression, fluoxetine is the only SSRI with FDA-approval and proven clinical efficacy in at least 3 clinical trials and should be considered the drug of choice. There is evidence supporting Zoloft® and Celexa® for this indication. Paroxetine should be considered last since it has a poor risk/benefit ratio.

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