Drug Class Review

28:16:04 Antidepressants

Selective Serotonin Reuptake Inhibitors

Citalopram (Celexa®)
Escitalopram (Lexapro®)
Fluoxetine (Prozac®, Prozac Weekly®, Sarafem®, Selfemra®)
Fluvoxamine (Luvox CR®)
Paroxetine HCl (Paxil®, Paxil CR®)
Paroxetine mesylate (Brisdelle® Pexeva®)
Sertraline (Zoloft®)

Serotonin/Norepinephrine Reuptake Inhibitor

Desvenlafaxine (Pristiq®, Khedezla)
Duloxetine (Cymbalta®, Irenka®)
Levomilnacipran (Fetzima®)
Milnacipran (Savella®)
Venlafaxine (Effexor®, Effexor XR®)

Combination Products

Fluoxetine/Olanzapine (Symbyax®)

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Executive Summary:

Introduction: The selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were developed to target serotonin receptors as well as norepinephrine for the SNRIs and to improve upon the safety of the tricyclic antidepressants (TCAs). Efficacy rates for the treatment of depression were similar to the TCAs with lower rates of adverse events and toxicity. Each of the SSRI agents, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and the SNRIs, desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine are available in oral formulations, including tablet, capsule, solution, suspension, and syrup. Extended/delayed release formulations of fluoxetine, fluvoxamine, paroxetine, desvenlafaxine, duloxetine, levomilnacipran and venlafaxine are available allowing for once-daily dosing of all agents except milnacipran (twice-daily dosing). Fluoxetine is additionally, available as a once-weekly, delayed-release capsule and in combination with olanzapine.

Indications: All the agents except milnacipran and fluvoxamine are indicated for treatment of major depressive disorders. Duloxetine is the only agent labeled for the treatment of chronic musculoskeletal pain and diabetic peripheral neuropathy pain. Fluoxetine/olanzapine is the only agent labeled for treatment-resistant major depressive disorder and depressed bipolar I disorder, fluoxetine is the only agent labeled to treat bulimia nervosa and paroxetine mesylate (Brisdelle) the only agent labeled for the treatment of abnormal vasomotor function in menopause. Other indications covered by this class of agents include anxiety disorders (generalized anxiety disorder, panic disorder, and social phobia disorder), obsessive-compulsive disorder, post-traumatic stress disorder and premenstrual dysphoric disorder.

Clinical Guidelines: Clinical guidelines for the pharmacotherapy of depression recommend the use of a second-generation antidepressant for the treatment of depression. Adjunctive treatment with another antidepressant or an atypical antipsychotic agent, is recommended in patients who are resistant to treatment. Guidelines for the treatment of obsessive-compulsive disorder consider Cognitive Behavior Therapy (CBT) or Exposure and Response Prevention therapy (ERP) first-line treatment modalities with serotonin reuptake inhibitors (SSRIs and SNRIs) recommended first-line for pharmacotherapy. Clomipramine may be more effective than serotonergic agents but adverse events are more significant, relegating it to second-line or augmentation use. Combination therapy with psychological counseling and medication therapy has been found most effective. Guidelines for the treatment of fibromyalgia suggest directing therapy toward the most troublesome symptoms. Amitriptyline, serotonin reuptake inhibitors (duloxetine, fluoxetine, milnacipran most commonly), pregabalin and traditional pain management strategies are recommended. Guidelines for treatment of depressive, bipolar I disorder suggest mood stabilizers may be adequate for depressive episodes and minimize the need for antidepressant therapy. Antipsychotic agents may be used alone or in combination with other mood stabilizers or antidepressants (e.g., fluoxetine/olanzapine) to maintain mood stability, control agitation or treat bipolar disorder in patients experiencing loss of efficacy with lithium therapy. Guidelines for the treatment of menopause suggest hormonal therapy first line. In women unable or unwilling to take hormonal therapy, SSRI, SNRI,

clonidine, gabapentin or pregabalin may be alternatives. Paroxetine and fluoxetine should not be used in women with a history of breast cancer receiving tamoxifen. Guidelines suggest that for treatment of premenstrual dysphoric disorder first-line pharmacotherapy includes SSRIs, venlafaxine and clomipramine. PTSD guidelines suggest first-line pharmacotherapy with SSRIs or SNRIs after or with a trial of trauma-focused psychological therapy. Guidelines recommend treatment of anxiety disorders with psychological interventions. First-line pharmacotherapy includes SSRIs, followed by SNRIs, pregabalin or monoamine oxidase inhibitors.

Clinical Efficacy: Clinical experience with the second-generation antidepressants has not identified a significant difference among agents for indications in which they are labeled. The majority of comparative evidence evaluated in this report comes from the Oregon Report, systematic reviews and meta-analyses. In pediatrics, only fluoxetine demonstrates a favorable risk:benefit profile. In adults, improvements in depression scores, response rates and remission rates did not differ between SSRIs and SNRIs and where evidence is available, no differences exist among agents.

Adverse Drug Reactions: The SSRI and SNRI agents were found to produce similar types of adverse reactions although the rates varied among individual agents. Venlafaxine has the highest rate of nausea and vomiting, paroxetine has more sexual dysfunction, sertraline has a higher rate of diarrhea, fluvoxamine has the highest mean adverse event incidence rate and venlafaxine results in more discontinuations of treatment due to adverse events. The SSRIs are associated with an increased risk of ischemic stroke. Risk of non-vertebral fractures is increased with SSRI use, which appears to be dose-dependent for citalopram, fluoxetine, paroxetine and sertraline. Gastrointestinal bleeding is increased with the use of SSRI/SNRI and increased with concomitant non-steroidal anti-inflammatory (NSAID) use. Sexual dysfunction is common with this class of antidepressants and most common with paroxetine and sertraline. Suicidality is increased in children and young adults but not adults. The risk of suicidal behaviors or thoughts is similar among agents. Increases in weight are more common with paroxetine than fluoxetine or sertraline.

Summary: Overall, the second-generation antidepressant SSRI and SNRI agents are effective treatment options for mental health disorders. When compared in clinical trials, the agents demonstrate similar rates of efficacy with varying rates of adverse effects. The second-generation antidepressant products are available in many dosage forms, offer once-daily dosing (except milnacipran) and are recommended in expert guidelines as first-line pharmacotherapy for many indications. Treatment of pediatric, adolescent and young adults must be undertaken with caution due to the risk of suicidal thoughts and behaviors. Treatment must be individualized for each patient, considering treatment history, disease severity, comorbid conditions, age, adverse effect profile, potential drug-drug interactions, patient preference, cost and accompanied by patient education and close monitoring during the initial month of therapy.

Introduction:

The first antidepressant was discovered in the 1950s while researching treatments for schizophrenia.[1,2] Imipramine altered the brain's neurotransmitters and resulted in feelings of euphoria. Many other antidepressant medications with a similar three-ring chemical structure became available over the next decades. Unfortunately, these "tricyclic" antidepressant (TCA) agents also produced serious adverse effects including: somnolence, anticholinergic effects and overdose deaths.[3] In the 1980s, the development of a more targeted class of antidepressant medications, known as selective serotonin reuptake inhibitors (SSRIs), provided safer options for patients with mental health disorders. The SSRIs demonstrated rates of efficacy similar to the TCAs with reduced rates of adverse effects and lower risk of death from overdose. By 1990, fluoxetine (Prozac®), an SSRI antidepressant, was listed as one of the most highly prescribed medications in the US, with ~65,000 prescriptions filled monthly and over $1 billion in annual sales.[1,4] In 2002, antidepressants comprised the third largest class of US prescription sales (10.9 billion) with serotonergic agents accounting for 57.6% of this market.[5] The development of new antidepressant agents with varying neurotransmitter selectivity and unique mechanisms of action continues today with the goal of creating highly effective and safe therapeutic treatment options.

As a class, the antidepressant agents are indicated in the treatment of a variety of mental health disorders (including depression, anxiety and other mood disorders) as well as some non-psychiatric conditions (including musculoskeletal pain, neuropathies, fibromyalgia, insomnia and tobacco abuse).[6-9] The antidepressants may be categorized into different subclasses depending on structure, mechanism of action or serotonergic activity including: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin-reuptake inhibitors (SRIs), selective serotonin-and-norepinephrine reuptake inhibitors (currently designated SNRIs), serotonin-and-norepinephrine-reuptake inhibitors (SNRIs), serotonin modulators and miscellaneous agents. These agents are Food and Drug Administration (FDA) approved for various indications, have varying mechanisms of action and differ in rates of adverse events/drug interactions.[6,7] This report will focus on the selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) and serotonin-norepinephrine reuptake inhibitors (desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine) All of these agents are available in oral formulations, including tablet, capsule, solution, suspension and syrup. Extended/delayed release formulations of fluoxetine, fluvoxamine, paroxetine, desvenlafaxine, duloxetine, levomilnacipran and venlafaxine are available allowing for once-daily dosing of all agents except milnacipran (twice daily dosing). Fluoxetine is additionally available as a once-weekly, delayed-release capsule and as a capsule in combination with olanzapine. Each of the medications is labeled for use in the treatment of mental health disorders.[8,9] See Table 1 for a summary of the included agents. With the exception of milnacipran and fluvoxamine all agents carry an indication for treatment of major depressive disorder. Duloxetine is the only agent FDA-approved for the treatment of chronic musculoskeletal pain and diabetic peripheral neuropathy pain. Fluoxetine/olanzapine is the only agent approved for treatment resistant major depressive disorder and depressed bipolar I disorder, fluoxetine is the only agent approved to treat bulimia nervosa, and paroxetine mesylate (Brisdelle) is the only agent approved for the treatment of abnormal vasomotor function in menopause. See Table 2 for the labeled indications of each of the agents.

Table 1: Comparison of Agents [10-27]

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Selective Serotonin Reuptake Inhibitors					
Citalopram (Celexa®)	Oral Solution: 10 mg/5 mL Oral Tablet: 10 mg, 20 mg, 40 mg Celexa Oral Tablet: 10 mg, 20 mg, 40 mg	Depression **Off-label Use** Alcoholism, Coronary arteriosclerosis – Depression, Obsessive-compulsive disorder Panic disorder Postmenopausal flushing Premenstrual dysphoric disorder	Depression • Initial: 20 mg daily (morning or evening), increase weekly by 20 mg; MAX: 40 mg daily • Max Dose: 40 mg daily due to risk of QT prolongation	Not Established	Yes
Escitalopram (Lexapro®)	Oral Solution: 5 mg/5 mL Oral Tablet: 5 mg, 10 mg, 20 mg Lexapro Oral Solution: 5 mg/5 mL Oral Tablet: 5 mg, 10 mg, 20 mg	Generalized Anxiety Disorder Major Depressive Disorder **Off-label Use** Cerebrovascular accident - Depression; Prophylaxis Mixed anxiety and depressive disorder Obsessive-compulsive disorder	Generalized anxiety disorder • Initial: 10 mg daily (morning or evening) • Maintenance: 10 mg daily, after 1 week may increase to 20 mg daily Major depressive disorder • Initial: 10 mg daily (morning or evening) • Maintenance: 10 mg daily, after 1 week may increase to 20 mg daily	Major depressive disorder Age ≥ age 12 years: • Initial: 10 mg daily (morning or evening) • Maintenance: 10 mg daily, may increase to 20 mg daily after 3 weeks	Yes

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		Panic disorder Premenstrual dysphoric disorder	Cerebrovascular accident - Depression; Prophylaxis • Age ≤ 65 years: 10 mg daily • Age > 65 years; 5 mg daily Mixed anxiety and depressive disorder • 10-20 mg daily Obsessive-compulsive disorder • 10-20 mg/day Panic disorder • Study dosing, mean 10.8 mg daily Premenstrual dysphoric disorder • Day 1: 5 mg, Day 2: 10 mg, then 20 mg daily (1st day ovulation until first day menstruation)		
Fluoxetine (Prozac®, Prozac Weekly®, Sarafem®, Selfemra®)	Oral Capsule: 10 mg, 20 mg, 40 mg Oral Capsule, Delayed Release: 90 mg Oral Solution: 20 mg/5 mL Oral Syrup: 20 mg/5 mL Oral Tablet: 10 mg, 20 mg Fluoxetine HCl Oral Tablet: 60 mg	Bulimia nervosa Depressed bipolar I disorder (adjunctive with olanzapine) Major depressive disorder Major depressive disorder, Treatment resistant (adjunctive with olanzapine) Obsessive-compulsive disorder Panic disorder Premenstrual dysphoric disorder	Bulimia nervosa • 60 mg daily in the morning • May titrate to this dose Depressed bipolar I disorder (adjunctive with olanzapine): Pulvule • Initial: 20 mg daily with olanzapine 5 mg in the evening • Titrate to tolerability/clinical effect (range: fluoxetine 20 to 50 mg & olanzapine 5 to 12.5 mg in the evening) Major depressive disorder: Capsule, Solution • Initial: 20 mg daily, after several weeks may increase dose	Depressed bipolar I disorder (adjunctive with olanzapine): Pulvule Age: 10-17 years: • Initial: 20 mg daily & olanzapine 2.5 mg in the evening • Titrate to tolerability/clinical effect Major depressive disorder: capsule, solution Age ≥ 8 years: • Initial: 10 to 20 mg daily • Lower-weight children: Initial: 10 mg daily, may increase to 20 mg daily after several weeks if inadequate response	Yes

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Prozac Oral Capsule: 10 mg, 20 mg, 40 mg Prozac Weekly: Oral Capsule, Delayed Release: 90 mg Sarafem: Oral Tablet: 10 mg, 20 mg	**Off-label Use** Body dysmorphic disorder Cancer - Depression Depression - Diabetes mellitus Dysthymia Fibromyalgia Hot sweats Posttraumatic stress disorder Raynaud's phenomenon	• Full Therapeutic effect may be delayed 4 weeks or more Max: 80 mg daily Capsule, Delayed-Release • Convert from 20 mg daily to 90 mg weekly 7 days after last 20 mg dose • Major depressive disorder, Treatment resistant (adjunctive with olanzapine): Pulvule Initial: 20 mg daily with olanzapine 5 mg in the evening • Titrate to tolerability/clinical effect (range: fluoxetine 20-50 mg & olanzapine 5-20 mg in the evening) Obsessive-compulsive disorder • Initial: 20 mg daily in the morning • Maintenance: 20-60 mg daily; MAX 80 mg daily Panic disorder • Initial: 10 mg daily x 7 days, then increase to 20 mg • 60 mg daily, maximal studied dose Premenstrual dysphoric disorder, tablets • 20 mg daily continuously • OR • 20 mg daily from 14 days prior to menses to menses • MAX: 80 mg daily	Obsessive-compulsive disorder Age ≥ 7 years: • Initial: 10 mg daily, after 2 weeks increase dose to 20 mg; usual range: 20-60 mg daily ○ Lower-weight children: Ad above, range: 20-30 mg daily	

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Fluvoxamine (Luvox CR®)	Oral Capsule, Extended Release: 100 mg, 150 mg Oral Tablet: 25 mg, 50 mg, 100 mg Luvox CR Oral Capsule, Extended Release: 150 mg	Obsessive-compulsive disorder **Off-label Use** Depression Eating disorder Panic disorder Social phobia	Depression • 50 to 300 mg/day Obsessive-compulsive disorder • Immediate-release: 50 mg daily at bedtime, increase every 4-7 days by 50 mg to therapeutic range 100-300 mg daily; MAX 300 mg daily • Extended-release: 100 mg daily at bedtime, increase every 4-7 days by 50 mg to MAX dose 300 mg daily • 100 mg/day at bedtime; may increase by 50 mg increments every week to therapeutic range 100-300 mg daily to MAX 300 mg daily Social phobia • Extended-release: 100 mg daily at bedtime, increase weekly by 50 mg to therapeutic range 100-300 mg daily to MAX 300 mg daily	Obsessive-compulsive disorder Age 8-11 years • Immediate-release: 25 mg daily at bedtime, increase every 4-7 days to therapeutic range 50-200 mg daily: MAX 200 mg daily Age 12-17 years • Immediate-release: 25 mg daily at bedtime, increase every 4-7 days to therapeutic range 50-200 mg daily: MAX dose 300 mg daily	Yes
Paroxetine Hydrochloride (Paxil®, Paxil CR®)	Oral Tablet: 10 mg, 20 mg, 30 mg, 40 mg Oral Tablet, Extended Release: 12.5 mg, 25 mg, 37.5 mg	Generalized anxiety disorder Major depressive disorder Obsessive-compulsive disorder	Generalized anxiety disorder • 20 mg daily in the morning, increase weekly by 10 mg dose Major depressive disorder	Not established	Yes

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Paxil CR Oral Tablet, Extended Release: 12.5 mg, 25 mg, 37.5 mg Paxil Oral Suspension: 10 mg/5 mL Oral Tablet: 10 mg, 20 mg, 30 mg, 40 mg	Panic disorder Posttraumatic stress disorder Premenstrual dysphoric disorder Social phobia **Off-label Use** Drug-induced depressive state Fibromyalgia Hot sweats Premature ejaculation	• Immediate-release: 20 mg daily in the morning, increase weekly by 10 mg dose: MAX 50 mg/day • Controlled-release: 25 mg daily in the morning, increase weekly by 12.5 mg dose to MAX 62.5 mg daily Obsessive-compulsive disorder • 20 mg daily in the morning, increase weekly by 10 mg dose to usual effective dose of 40 mg daily; MAX 60 mg daily Panic disorder • Immediate-release: 10 mg daily in the morning, increase weekly by 10 mg dose to usual effective dose of 40 mg daily; MAX 60 mg daily • Controlled-release: 12.5 mg/day in the morning, increase weekly by 12.5 mg dose to MAX dose 75 mg/day Posttraumatic stress disorder • 20 mg daily in the morning, increase weekly by 10 mg dose to usual effective dose of 20 mg daily Premenstrual dysphoric disorder • Controlled-release: 12.5 mg daily in the morning, may increase after one week to 25 mg daily		

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
			(throughout menstrual cycle or luteal phase only) Social phobia • Immediate-release: 20 mg daily • Controlled-release: 12.5 mg daily, may increase weekly to 12.5 mg dose to MAX dose 37.5 mg daily		
Paroxetine Mesylate (Brisdelle®, Pexeva®)	Brisdelle Oral Capsule: 7.5 mg Pexeva Oral Tablet: 10 mg, 20 mg, 30 mg, 40 mg	Abnormal vasomotor function in Menopause (moderate to severe) Generalized anxiety disorder Major depressive disorder Obsessive-compulsive disorder Panic disorder	Abnormal vasomotor function • Brisdelle 7.5 mg daily at bedtime Generalized anxiety disorder • Pexeva: Initial: 20 mg daily, may increase weekly by 10 dose Major depressive disorder • Pexeva: Initial: 20 mg daily, may increase weekly by 10 mg dose to MAX dose 50 mg/day Obsessive-compulsive disorder • Pexeva: Initial: 20 mg daily, may increase weekly by 10 mg dose to 40 mg daily; MAX 60 mg daily Panic disorder • Pexeva: Initial: 10 mg daily, increase weekly by 10 mg dose to 40 mg daily; MAX 60 mg/day	Not established	No
Sertraline (Zoloft®)	Oral Solution: 20 mg/1 mL Oral Tablet: 25 mg, 50 mg, 100 mg	Major depressive disorder Obsessive-compulsive disorder	Dysthymia • 50 mg daily; MAX 200 mg daily Major depressive disorder	Obsessive-compulsive disorder Age 6-12 years	Yes

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Zoloft Oral Solution: 20 mg/1 mL Oral Tablet: 25 mg, 50 mg, 100 mg	Panic disorder Posttraumatic stress disorder Premenstrual dysphoric disorder Social phobia **Off-label Use** Bipolar disorder, depressed phase (adjunctive) Depression – Post-Myocardial infarction Dysthymia Fibromyalgia Generalized anxiety disorder Night eating syndrome Severe major depression with psychotic features (Adjunctive)	• 50 mg daily, may increase weekly to MAX 200 mg daily Obsessive-compulsive disorder • 50 mg daily, may increase weekly to MAX 200 mg daily Panic disorder • 25 mg daily for 7 days, then increase to 50 mg daily, then increase dose weekly to MAX dose 200 mg daily Posttraumatic stress disorder • 25 mg daily for 7 days, then increase to 50 mg daily, then increase dose weekly to MAX dose 200 mg daily Premenstrual dysphoric disorder • During menstrual cycle: 50 mg daily, may be increased by 50 mg doses to 150 mg daily • Luteal phase dosing: 50 mg daily, may increase to 100 mg daily after 3 days (each luteal phase) Social phobia • 25 mg daily for 7 days, then 50 mg daily, then may increase weekly to MAX dose 200 mg daily	• 25 mg daily, may increase weekly to MAX dose 200 mg daily Age 13-17 years • 50 mg daily, may increase weekly to MAX dose 200 mg daily	
Serotonin/Norepinephrine Reuptake Inhibitors					
Desvenlafaxine (Khedezla®, Pristiq®)	Oral Tablet, Extended Release: 50 mg, 100 mg	Major depressive disorder	Major depressive disorder • 50 mg daily • Swallow whole	Not established	Yes

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Khedezla Oral Tablet, Extended Release: 50 mg, 100 mg Pristiq Oral Tablet, Extended Release: 25 mg				
Desvenlafaxine succinate (Pristiq®)	Pristiq Oral Tablet, Extended Release: 50 mg, 100 mg	Major depressive disorder **Off-label Use** Menopausal flushing	Major depressive disorder • 50 mg daily • Swallow whole Menopausal flushing • 100 mg daily	Not established	No
Duloxetine (Cymbalta®, Irenka®)	Oral Capsule, Delayed Release: 20 mg, 30 mg, 40 mg, 60 mg Cymbalta Oral Capsule, Delayed Release: 20 mg, 30 mg, 60 mg Irenka	Diabetic peripheral neuropathy - Pain Fibromyalgia Generalized anxiety disorder Major depressive disorder Musculoskeletal pain, Chronic **Off-label Use**	Diabetic peripheral neuropathy – Pain • 60 mg daily Fibromyalgia • Initial: 30 mg daily for 7 days, then increase to 60 mg daily as tolerated Generalized anxiety disorder • 60 mg daily (may start with 30 mg) for 7 days then increase by 30 mg weekly to MAX 120 mg daily	Generalized anxiety disorder Age ≥ 7 years: 30 mg daily for 14 days, may increase to 60 mg and to MAX dose 120 mg daily	Yes

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Oral Capsule, Delayed Release: 40 mg	Pain, Chemotherapy-induced - Peripheral nerve disease Urinary incontinence	Major depressive disorder • Initial: 20 mg twice daily, titrate to 60 mg daily (once or twice daily) • Maintenance: 60 mg daily, may increase to MAX 120 mg daily Musculoskeletal pain, Chronic • Initial: 30 mg daily for 7 days • Maintenance: 60 mg daily Pain, Chemotherapy-induced - Peripheral nerve disease • 30 mg daily for 7 days and increase to 60 mg daily Urinary incontinence • 40 mg twice a day		
Levomilnacipran (Fetzima®)	Fetzima Oral Capsule, Extended Release: 20 mg, 40 mg, 80 mg, 120 mg	Major depressive disorder	Major depressive disorder • Initial: 20 mg daily for 2 days, then 40 mg, may increase by 40 mg every 2 days to MAX 120 mg daily	Not established	No
Milnacipran (Savella®)	Savella Oral Tablet: 12.5 mg, 25 mg, 50 mg, 100 mg	Fibromyalgia **Off-label Use** Depression	Fibromyalgia • Initial: 12.5 mg daily on day 1, then 12.5 mg twice daily on day 2-3, then 25 mg twice daily day 4-7 • Maintenance: 50 mg twice daily, MAX 100 mg twice daily	Not established	No
Venlafaxine (Effexor®, Effexor XR®)	Oral Capsule, Extended Release: 37.5 mg, 75 mg, 150 mg	Generalized anxiety disorder	Generalized anxiety disorder, Extended-release capsule	Not established	Yes

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Oral Tablet: 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg Oral Tablet, Extended Release: 37.5 mg, 75 mg, 150 mg, 225 mg Effexor XR Oral Capsule, Extended Release: 37.5 mg, 75 mg, 150 mg	Major depressive disorder Panic disorder, With or without agoraphobia Social phobia **Off-label Use** Attention deficit hyperactivity disorder Binging - Eating disorder Bipolar disorder, depressed phase Cerebrovascular accident - Depression Depression - Perimenopausal disorder Dysthymia Hot sweats, Breast cancer-related Menopausal flushing Obsessive-compulsive disorder Posttraumatic stress disorder Premenstrual dysphoric disorder	• Initial: 37.5-75 mg daily, may increase every 4 days by 75 mg dose to MAX 225 mg/day Major depressive disorder • Immediate-release, Outpatients: 75 mg daily (divided doses), may increase every 4 days to MAX dose 225 mg daily • Immediate-release, Inpatients: 75 mg daily (divided doses), may increase every 4 days to MAX 375 mg daily • Extended-release capsules and tablets: 37.5 to 75 mg daily, may increase every 4 days by 75 mg dose to MAX dose 225 mg/day Panic disorder, with or without agoraphobia (Extended-release capsule) • Initial: 37.5 mg daily, increase after 7 days to 75 mg daily, may increase weekly by 75 mg dose to MAX 225 mg daily Social phobia (Extended-release capsules and tablets) • 75 mg daily		

SSRI	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		Recurrent major depressive episodes; Prophylaxis Tension-type headache; Prophylaxis			
Combination Products					
Fluoxetine/Olanzapine (Symbyax®)	Oral Capsule: 25 mg-3 mg, 25 mg-6 mg, 25 mg-12 mg 50 mg-6 mg, 50 mg-12 mg Symbyax®: Oral Capsule: 25 mg-3 mg, 25 mg-6 mg, 25 mg-12 mg 50 mg-6 mg, 50 mg-12 mg	Bipolar disorder, depressed phase Major depressive disorder, Treatment-resistant	Bipolar disorder, depressed phase • Initial: 25 mg-6 mg once daily in the evening • Usual range: Fluoxetine 25 to 50 mg with Olanzapine 6 to 12 mg in the evening. • Safety of doses above 75 mg-18 mg have not been established. Major depressive disorder, Treatment-resistant • Initial: 25 mg-6 mg once daily in the evening • Usual range: Fluoxetine 25 to 50 mg with Olanzapine 6 to 18 mg in the evening • Safety of doses above 75 mg – 18 mg have not been established	Bipolar disorder, depressed phase Age 10 to 17 years: • Initial, 25 mg – 3 mg once daily in the evening • Usual range: Fluoxetine 25 to 50 mg with Olanzapine 6 to 12 mg daily in the evening • Safety of doses above 50 mg – 12 mg have not been established	Yes

Table 2: FDA-Labeled Indications of Antidepressant Agents

	Depression/Major Depressive Disorder	Major Depressive Disorder Treatment Resistant	Generalized Anxiety Disorder	Obsessive-Compulsive Disorder	Panic Disorder	Pre-menstrual Dysphoric Disorder	Post-Traumatic Stress Disorder	Social Phobia	Abnormal Vasomotor Function (menopause)	Bulimia Nervosa	Depressed Bipolar I Disorder	Diabetic Peripheral Neuropathy – Pain	Fibromyalgia	Musculoskeletal pain, chronic
Serotonin Reuptake Inhibitors														
Citalopram	X													
Escitalopram	X		X											
Fluoxetine	X			X	X	X				X				
Fluvoxamine				X										
Paroxetine **Paroxetine mesylate**	X		X	X	X	X	X	X	X					
Sertraline	X			X	X	X	X	X						
Serotonin/Norepinephrine Reuptake Inhibitor														
Desvenlafaxine	X													
Duloxetine	X		X									X	X	X
Levomilnacipran	X													
Milnacipran													X	
Venlafaxine	X		X		X			X						
Combination Products														
Fluoxetine & Olanzapine		X									X			

Disease Overview

Mental illness is defined as any diagnosable mental disorder with sustained abnormalities in behavior, mood or thinking that results in impaired functioning and distress.[28] Diagnosable mental disorders may include anxiety disorders, mood disorders, personality disorders, attention deficit disorders, schizophrenia, addiction disorders and feeding/eating disorders.[29] The most commonly reported mental illnesses in adults in the United States (US) are anxiety and mood disorders, including depression and bipolar disorder.[28] The most commonly reported mental illnesses in adolescents in the US are depression and attention deficit disorders.[30] All mental illnesses can cause severe disruptions in activities of daily living and result in premature death. According to the World Health Organization (WHO), mental health disorders cause more patient disability than cancer, heart disease or any other illness.[28] In addition, mental health disorders are associated with increased rates of comorbid chronic diseases (including cardiovascular disease, diabetes, obesity, asthma, epilepsy and cancer), inappropriate use of medical care (including treatment nonadherence and increased emergency department visits), use of tobacco products, abuse of alcohol and other substances, increased rates of intentional and unintentional injuries and an overall increase in adverse health outcomes.[28] According to the Centers for Disease Prevention and Control (CDC), approximately 25% of all adults currently have a mental illness and up to 50% of adults will report a mental illness during their lifetime resulting in an economic burden of nearly $300 billion in the US (2002).[28] Increased access to mental health treatment services results in successful management of the mental health disorder, reduced rates of morbidity, mortality and improved health outcomes for comorbid chronic diseases.[28]

Major Depressive Disorder

The mood disorders (including major depressive disorder; bipolar I disorder; bipolar II disorder; cyclothymic disorder; persistent depressive disorder (dysthymia); premenstrual dysphoric disorder) affect approximately one in ten adult Americans.[31] Major depressive disorder is the most common of the mood disorders, affecting nearly 15% of US adults.[32] In 2004, depression was listed as having the third-largest disease burden across the world. [33] In general, depression occurs more frequently in women than men, in the 40-59-year age range and in patients living below the poverty level. Depressive disorder is linked to increased rates of chronic disease, health care utilization and impaired activities of daily living. Almost half of all patients with depression experience an inability to maintain healthy work, home and social habits. The economic burden of depression in the US (~$83.1 billion in 2000) results from the combined costs associated with increased rates of indirect costs (unemployment, lost productivity, etc.) in addition to direct healthcare costs.[30,34] Depression is frequently underdiagnosed and, even more frequently, depression is inadequately treated. Improving disease education and increasing access to care will help to improve clinical outcomes and save costs.[29]

A Behavioral Health Barometer for Utah by the Substance Abuse and Mental Health Services Administration (SAMHSA) reveals that, compared to the US as a whole, both Utah youth ages 12-17 and adults were more likely to have a major depressive episode. For youth the rate of a major depressive disorder in Utah vs. the US during 2011/12 was 10.2% vs. 8.7% and in 2012/13 it was 11.5% vs. 9.9%. For adults over the same two time periods the rates were 5.1% vs. 4% and 5.4% vs. 4.1%, respectively).[35]

Depression is a serious mental disorder characterized by changes in cognitive function and physical behaviors with a loss of pleasure in enjoyable activities.[29] Major depression is defined as the presence of at least 5 symptoms during a period of at least 2-weeks that reflect a change in previous functioning and that cause distress or impairment in normal activities. Symptoms associated with a depressive episode must include sadness and/or loss of interest or pleasure and may also include significant unexplained weight loss, insomnia or hypersomnia, agitation, fatigue, feelings of worthless, excessive guilt, reduced ability to concentrate and recurrent thoughts of death. In <2% of the general population depression is not clearly associated with acute distress, impairment or change from previous functioning. Dysthymic disorder is defined as a persistent depressive mood with chronic ($\geq$2 years), ongoing symptoms which tend to be less severe and/or numerous.[29]

Drug therapy is the foundation of the medical management of the mood disorders. Before the introduction of the second-generation antidepressants, drug therapy was limited to tricyclic antidepressants and monoamine oxidase inhibitors, known collectively as the first-generation antidepressants. The first generation antidepressants are associated with many intolerable adverse effects (sedation and anticholinergic effects) and are no longer agents of choice for treating depressive disorders. As a result, the second-generation antidepressants, including the selective serotonergic agents and serotonin modulators, have become one of the most commonly prescribed drug classes in the US pharmaceutical market accounting for $10.9 billion in US prescription sales in 2003.[30] Clinical evidence suggests the most efficacious treatment for depression includes a combination of psychological therapy and medication therapy for at least 6-8 weeks. The treatment plan should reduce the risk of disease/symptom recurrence.[30] A response rate of 70% may be achieved with 6-8 weeks of most any pharmacotherapy. Titration schedules should be conservative, with modest increases from the initial dose each 3 weeks to allow for a clinical response as opposed to aggressively increasing doses, which may reduce tolerability and increase adverse events. Patience is key to successful outcomes because it may take 12 weeks for substantial benefit. Treatment is generally continued for 6 to 12 months after stabilization. Almost half of all patients being treated for depression by their primary care provider will discontinue their medication therapy within a month, unless proper education and a treatment plan is provided. There is little evidence to demonstrate one agent or class of antidepressants is more effective than others. Selection of an antidepressant agent should be based on treatment history, comorbid conditions, anticipated side effects, clinical evidence and patient preference.[4,30] In patients demonstrating suicidal ideation, the drug selected should have low toxicity if taken in overdose.[30]

Clinical guidelines for the treatment of depression include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders (2013)[36], the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010)[37], the National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)[38] and American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007).[39] See Table 3 for a summary of the most current guideline recommendations. In general, the guidelines recommend use of a second-generation antidepressant for the treatment of depression. First-line agents should include those for which the patient has had a previous positive response or a

family history of a positive response. If only a partial response is achieved at 6-8 weeks, referral to a mental health specialist is recommended. Partial responders should receive an alternative antidepressant, a combination of antidepressant agents or adjunctive treatment with another class of medications including lithium, thyroid hormone, atypical antipsychotic agents or dopamine agonists. A large randomized controlled trial examining Sequenced Treatment Alternatives to Relieve Depression (STAR*D) reported no differences in efficacy between the adjunctive medication classes.[40] Medication therapy should be adjusted until a full remission is achieved. Treatment should be continued for an additional 6-9 months to prevent relapse. Chronic maintenance therapy is recommended in patients with two or more depression episodes. Cognitive Behavioral Therapy (CBT) is recommended for all patients with depressive disorders.[29] Table 3 presents the current practice guidelines.

Table 3. Current Clinical Practice Guidelines for the Treatment of Depressive Disorders

Guideline	Recommendations
World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorder (2013)[36]	Medication therapy in combination with psychological counseling is recommended A treatment plan and disease/medication education are recommended for all patients First-line: Antidepressants No single class of antidepressants has proven to be more effective than another Amitriptyline, clomipramine and venlafaxine have demonstrated increased efficacy in severely depressed hospitalized patients Newer agents (bupropion, trazodone, SSRI, SNRIs, mirtazapine) are generally better tolerated than the older agents In treatment-resistant patients: Consider increasing the dose, switching to another antidepressant agent, combining two antidepressants, augmenting the antidepressant with another agent (best evidence for aripiprazole, lithium, quetiapine)
National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)[38]	Mild-Moderate Disorder First-line: low-intensity psychosocial intervention Second-line: antidepressant therapy (typically SSRI) OR a high-intensity psychosocial intervention Moderate-Severe Disorder First-line: combination antidepressant therapy and a high-intensity psychological intervention Antidepressant agents • SSRIs have a favorable risk-benefit ratio • Fluoxetine, fluvoxamine and paroxetine are associated with increased risk of drug interactions • Venlafaxine and tricyclic antidepressants are associated with increased risk of death from overdose • Monoamine oxidase inhibitors (MAOIs) should only be prescribed by specialists

Guideline	Recommendations
	• In treatment-resistant patients, increase dose or switch to another antidepressant

American Psychiatric Association (APA): Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010) [37]	Acute phase
	First-line: antidepressant medication (SSRI, SNRI, bupropion, mirtazapine
	• The effectiveness of antidepressant medications is comparable and initial selection is based on adverse effect profile, prior treatments, cost and patient preference
	  ○ If side effects occur, lower dose or switch agents
	  ○ If no response or partial response: increase dose, switch agents or augmenting the antidepressant with another antidepressant or a non-antidepressant medication (lithium, thyroid hormone or a second generation antipsychotic)
	
	Continuation phase
	Continue successful treatment for 6-9 months and monitor for signs of relapse
	
	Maintenance phase
	Continue successful treatment in patients with three or more depressive episodes or with additional risk factors for relapse
	
	Discontinuation of treatment
	Taper the medication over the course of at least several weeks
	
	Other notes
	Combination of antipsychotic and antidepressant medications is recommended in patients with psychotic symptoms

Institute for Clinical Systems Improvement (ICSI): Major Depression in Adults in Primary Care (2011) [41]	Recommended pharmacotherapy: • SSRIs, venlafaxine, duloxetine, desvenlafaxine, mirtazapine, bupropion Other options: • Secondary amine tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs) Augmentation therapy: • Bupropion, buspirone, mirtazapine, triiodothyronine (T3), stimulants, TCA-SSRI combination, lithium, atypical antipsychotics Recommended in patients with treatment-resistant or partially-responsive disease: Referral to a mental health specialist
Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults (2009)[42]	Selection • Based on disease severity, comorbid conditions, adverse effect profile, treatment history, potential drug–drug interactions, patient preference and cost; Use of antidepressant should be accompanied by patient education, close monitoring (1-4 weeks) and self-management techniques First-line recommendations

Guideline	Recommendations
	Bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, sertraline, venlafaxine Second-line recommendations Amitriptyline, clomipramine and other tricyclic antidepressant (TCA) agents; quetiapine; selegiline; trazodone Third-line recommendations Phenelzine, tranylcypromine
American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007) [39]	A confidential relationship should be maintained with the child or adolescent Psychiatric assessments should routinely be made Treatment should always include an acute and continuation phase, some may require maintenance treatment First-line: Supportive psychotherapy Second-line: Psychotherapy and/or antidepressants ○ Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used pharmacotherapy in pediatric patients ○ Clinical response should be assessed at 4-week intervals ▪ If inadequate response, increase dose ○ Treatment should be continued for 6-12 months ○ Atypical antipsychotics, combined with SSRIs, are recommended as the treatment of choice for depressed psychotic pediatric patients

Key: SSRI – selective Serotonin Reuptake Inhibitor, serotonin norepinephrine reuptake inhibitor – SNRI

Obsessive-Compulsive Disorder (OCD)

Obsessive Compulsive Disorder (OCD) is a common, chronic anxiety disorder characterized by excessive, unrealistic worry about everyday events or tasks that can interfere with all aspects of life. Obsessions are persistent, unwanted, involuntary, intrusive, abnormal thoughts, ideas, urges or images. Compulsions are repeated, ritualized behaviors undertaken in an attempt to reduce or prevent the anxiety or distress an obsessive thought precipitates.[43-45 32,46] Most people are diagnosed with obsessive-compulsive disorder by age 19, although 25% exhibit symptoms by age 14.[44,46] Males present at an earlier age, in greater proportion and often with more severe disease; however, gender distribution in adults is equal or slightly favors females.[32,47] The Substance Abuse and Mental Health Services Administration (SAMHSA) estimates the 12-month prevalence of OCD in US adults at 1.2%, or affecting 2.2 million people. Up to fifty percent of cases are classified as severe.[44] The lifetime morbidity risk is 2.7%.[48] Often OCD occurs with anxiety, depression or body dysmorphic disorder.[46] Risk factors for the development of OCD, include genetics (first-degree relative), frontal cortex and subcortical brain structure abnormalities, prior exposure to trauma and post-Streptococcal infection (Pediatric

Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections [PANDAS]).[49]

Treatment modalities include psychotherapy, medications or a combination of both. The most effective medications are SSRIs, SRIs (e.g. clomipramine) and tricyclic antidepressants. The doses of antidepressants used for treating OCD are frequently higher than those used for the treatment of depression and the clinical response may be delayed (8-12 weeks). Antipsychotic medications may be tried in patients unresponsive to other therapies. Cognitive behavior therapy (CBT) or habit reversal training were shown as effective as medication therapy, while Exposure and Response Prevention (ERP) demonstrated efficacy in patients failing serotonergic medications.[46] Patients unresponsive to other therapies may be considered for deep brain stimulation, a newer, surgical treatment option.[50]

Clinical guidelines for the treatment of obsessive-compulsive disorder include American Academy of Child and Adolescent Psychiatry (AACAP)[48], the American Psychiatric Association (APA)[51], and the National Institute for Health and Care Excellence (NICE)[51]. First-line treatments for mild to moderate disease include cognitive behavior therapy CBT or ERP. For patients with severe disease, who prefer medication or are unable to participate in psychological therapies, treatment options include treatment with an SSRI, clomipramine or combination of medication and psychological interventions. Medication, with or without psychological therapy, can be augmented if needed with SSRI, SNRI, clomipramine or more intensive psychological intervention. Table 4 presents the clinical practice guidelines.

Table 4: Clinical Practice Guidelines for the Treatment of Obsessive-Compulsive Disorder

Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder[49] (2012)	Clinicians should screen for obsessions, compulsions or repetitive behaviors • In the presence of symptoms, perform a full evaluation using DSM-IV criteria and scalar assessment • Perform a complete psychiatric evaluation • Perform a full medical, developmental, family, school history and psychiatric history and exam <u>First-line treatment for mild-to-moderate</u> cases • Cognitive behavior therapy/exposure and response prevention <u>First-line treatment in moderate-to-severe disease</u> • Cognitive behavior therapy and medication <u>First-line medications</u> • Serotonin reuptake inhibitors in children • Clomipramine, sertraline, fluvoxamine, fluoxetine, paroxetine • Use according to the American Academy of Child and Adolescent Psychiatry guidelines to monitor response, tolerability and safety. Selection of treatment should be guided by empirical evidence on moderators and predictors of treatment response • Consider comorbidities, family history In severe cases or those without a clinical response to CBT at several months, consider multimodal therapy (CBT and medication) • Combined therapy yielded the best effect on symptom score and remission rate

- Recommended based on a trial with sertraline, however, it is reasonable to extrapolate to any medication with efficacy in OCD

Medication augmentation strategies are indicated for resistant cases with moderate impairments in at least one domain of function despite adequate monotherapy

- Definitions
- Treatment resistant: Two medication trial failures (2 SSRIs or 1 SSRI and 1 clomipramine trial) and nonresponsive to cognitive therapy
  - Medication failure: 10 weeks medication at maximal or maximally tolerated doses with no change in last 3 weeks.
  - Nonresponse to cognitive therapy:
    - CBT: 8-10 sessions without improvement
    - E/RP: 6-8 sessions without improvement
- Partial responders – At least 3-weeks stable, persistent (moderate or worse) OCD symptoms at a maximal SSRI dose or demonstrated a flat dose-response curve or experienced adverse effects with increased dose
  - Clinicians should consider: Has patient received an adequate dose trial, whether maximum dose, maximally tolerated dose and if the dosage has been stable for 3 weeks and the trial extending at least 10 weeks.

Medication Augmentation strategies

- Add clomipramine (25-75 mg/day) to an SSRI (most synergy documented with fluvoxamine)
  - Fluvoxamine inhibits clomipramine metabolism. Use of fluoxetine or paroxetine with the combination may increase clomipramine toxicity and EKG effects due to CYP2D6 inhibition.
- Expert opinion:
  - Venlafaxine and duloxetine (inhibit monoamine uptake with fewer cardiovascular adverse effects)
  - Clonazepam and SSRIs (caution in younger children)
  - Atypical neuroleptics (based on data in adults, e.g. haloperidol, risperidone)
    - May be particularly useful in the setting of tic disorders, poor insight, pervasive developmental disorder symptoms and mood instability.
- Novel augmentation (not for routine use): Stimulants, gabapentin, sumatriptan, pindolol, inositol, opiates, St. John's Wort, N-acetyl cysteine and the glutamate antagonists memantine and riluzole

PANDAS cases of OCD: Standard treatments to address both OCD and streptococcal infections

Unproven: Therapeutic plasma exchange, intravenous immunoglobulin, D-cycloserine (effective in adults)

Consider psychosocial treatments

In patients with chronic tic or Tourette's disorders, ADHD, major depression/mood disorders, bipolar disease Pharmacotherapy for comorbid disorders: Pharmacotherapy

Practice guideline for the treatment of patients with obsessive-compulsive disorder[52] (reaffirmed 2012)	Psychiatric Management
	• Establish a therapeutic alliance, assess symptoms, use rating scales, enhance the safety or patient and others, complete psychiatric assessment, establish goals for treatment, establish the appropriate treatment setting, enhance adherence to treatment
	
	Choose Initial Treatment Modality
	• First-line treatment options (consider nature and severity of symptoms, co-occurring psychiatric/medical conditions and treatments, availability of CBT, past treatment history, current medications, capacities and preferences).
	  ○ Cognitive behavior therapy is first-line with mild symptoms of depression, anxiety illness, willingness to do the work of CBT or the patient prefers no medication
	  ○ SRI for those patients unable to cooperate with CBT, a history of SRI response, patient prefers SRI alone or in severe OCD where medication use may reduce symptoms allowing CBT
	  ▪ In pregnancy/breast-feeding perform a risk/benefit assessment
	  ○ Combination – unsatisfactory response to monotherapy, co-occurring psychiatric conditions where SSRIs are effective, those wishing to limit the duration of SSR
	
	Choosing Pharmacotherapy
	• First-Line: SSRIs that are FDA approved: fluoxetine, fluvoxamine, paroxetine, sertraline (via authors: citalopram and escitalopram also appear effective)
	  ○ Selection should be based on safety and acceptability of side effect profile, FDA warnings, drug interaction potential, past treatment response and presence of co-occurring medical conditions.
	• Clomipramine (meta-analysis showed indirect superiority over SSRIs but head-to-head trials do not support this and SSRIs have fewer safety issues)
	
	Choosing Psychotherapy
	• Evidence is strongest for CBD with behavioral techniques (e.g. exposure and response prevention). Useful in specific settings, cognitive techniques, psychoanalysis, dynamic psychotherapy, motivational interviewing, family therapy.
	
	Implementation of Pharmacotherapy
	• Start with manufacturers recommended regimen. Lower initial doses if adverse effects are of concern (split tablet, liquids)
	• Clinical improvement begins by 4-6 weeks, may require 10-12 weeks
	• Up-titrate dose weekly per manufacturer recommendation for first month. Dose may be increase to maximum recommended or tolerated dose every 1-2 weeks if response is sub-optimal at 4 weeks. Continue for 6 weeks. Higher doses produce higher response rates.
	  ○ Closely monitor for side effects including serotonin syndrome
	  ○ Elderly should be started at lower doses and titrated more cautiously

	Monitoring Adverse Events
	• Regularly inquire about side effects and manage actively
	  ○ Gastrointestinal distress – start with low doses and titrate slowly
	  ○ Insomnia – add a sleep-promoting agent
	  ○ Fatigue/sleepiness – consider modafinil
	  ○ Sweating – low-dose anticholinergic
	  ○ Sexual effects – reduce dose, wait for symptoms to remit, try once-weekly dosing or drug holiday before sexual activity, try a different SSRI, add bupropion
	
	Cognitive-Behavioral Therapies: May use individual, group, family sessions of up to 2 hours at least weekly. Twice weekly yields better results.
	• Expert consensus recommends 13-20 weekly sessions
	  ○ Booster sessions if severely ill, history of relapse or with signs of relapse. Self-help treatment guides are available.
	
	Lack of good response: Consider co-occurring conditions, adherence to treatment, psychosocial stress, family issues, inability to tolerate psychotherapy or maximal drug doses
	• Pharmacotherapy changes
	  ○ Try alternative SSRI (venlafaxine least likely to be helpful)
	  ○ Try switch from SSRI to mirtazapine
	  ○ Augment with antipsychotic medication or CBT
	• Consider augmentation strategies
	  ○ Augment SSRIs with trials of different antipsychotic medication or CBT (using ERP) or augmenting CBT with an SSRI, add booster sessions of cognitive therapy
	  ○ Combination SSRI/CBT reduces relapse
	• Continued poor response, consider augmentation of SSRI with clomipramine (monitor central nervous system and cardiovascular side effects), buspirone, pindolol, riluzole, once-weekly oral morphine sulfate (monitor misuse), D-amphetamine, tramadol, monoamine oxidase inhibitors, ondansetron, transcranial magnetic stimulation, deep brain stimulation, intensive residential treatment/partial hospitalization, ablate neurosurgery
	
	Discontinuing active treatment should be delayed 1-2 years. For most, continuation of some treatment is indicated.
	• Initiate medication discontinuation with a dose reduction of 10-25% every 1-2 months and observe for symptom recurrence/exacerbation.
	• Initiate ERP discontinuation with monthly booster sessions for 3-6 months , or more intensively as indicated.

NICE: Obsessive-compulsive disorder and body dysmorphic disorder: treatment [CG31] (2005)[53]	Mild impairment or prefers no medication • CBT (including ERP) Mild impairment in persons unable to engage in CBT (including ERP) or in which CBT has not been effective • SSRI (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) ○ IF partial response at 4-6 weeks, increase dose

	• More intensive CBT (including ERP) Moderate functional impairment • SSRI (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) ○ IF partial response at 4-6 weeks, increase dose • More intensive CBT (including ERP) Severe functional impairment • Combined SSRI and CBT (including ERP) Do NOT use tricyclic antidepressants (except clomipramine), SSRIs, SNRIs, MAOIs, anxiolytics, antipsychotics unless the patient has comorbidities

Abbreviations: CBT = cognitive behavioral therapy, SSRI = selective serotonin reuptake inhibitor, SRI = serotonin reuptake inhibitor, ERP = exposure and response prevention therapy, SNRI = serotonin/norepinephrine reuptake inhibitor

Fibromyalgia Disease Overview

The American College of Rheumatology defines fibromyalgia as a chronic, generalized, musculoskeletal disorder involving widespread bilateral pain affecting the upper body, lower body and spine.[54] Diagnostic criteria requiring the presence of ≥11 of 18 tender points was replaced in 2011 with a widespread pain index >7 with symptom severity scores >5 or widespread pain index of 3-6 with symptom severity score >9.[34] The etiology of fibromyalgia remains unclear. Neuroendocrine findings include elevated levels of cytokines. It is believed that peripheral pain stimuli lead to pain amplification resulting in a sustained sensitized state, centrally.[34] Symptomatology is variable but often includes fatigue, muscle pain (often characterized as burning), weakness, memory problems, paresthesia, cognitive disturbances, headaches, depression, insomnia and point tenderness that fluctuate in intensity over time.[55-57] Symptoms are often worsened by humidity, cold weather, over-activity and fatigue. Fibromyalgia currently has no cure and symptoms do not fully resolve even with treatment. A key to long-term management includes patient education concerning the disease and participation to achieve the benefits that may be achieved with lifestyle changes, regular exercise and medication management.[56] Fibromyalgia affects 2 to 4% of the population, is most prevalent in people aged 35 to 50 years and affects more women than men.[57] Fibromyalgia is often misdiagnosed. The actual prevalence is believed to be higher.[55] Disability rates are reported up to 46%. Direct and indirect health care costs are higher in patients with fibromyalgia.[56]

Treatment consists of self-care (physical exercise, stress management, relaxation techniques), various modalities of therapy (support, cognitive behavioral therapy, biofeedback, chiropracty, hydrotherapy, stretching, exercise therapy, massage or acupuncture) and the use of medications from a wide variety of pharmacologic classes (analgesic, antidepressant, anticonvulsant, and muscle relaxant). Patients should be referred for specialist assessment and care as appropriate. Patient satisfaction in managing this life-long disease may be improved by encouraging them to define their long-term management goals and specifically directing treatment toward the symptoms of most concern to them. Treatment outcomes are assessed by reducing key symptoms (e.g. pain, fatigue, insomnia, cognitive dysfunction) and improving quality-of-life.

Clinical guidelines for the management of fibromyalgia include recommendations from a systematic review in 2004 by Goldenberg[53] which became the basis of the UpToDate recommendations[56], the Scottish Intercollegiate Guidelines Network (SIGN) (2013),[57] Canadian

National Guidelines supported by the Canadian Pain Society and the Canadian Rheumatology Association[55], the European League Against Rheumatism (EULAR)[58], the Veteran's Affairs/Department of Defense guideline[59], German National Guidelines[60] all recommend initial patient education concerning the disease, the waxing and waning course of symptoms, the importance of goal setting, self-care and involvement in coping skills, stress reduction, activity and exercise. Treatment should address the most troublesome symptoms to the patient. Cognitive behavior therapy may have a role. The most commonly recommended medications for multi-symptom illness include tricyclic antidepressants (low dose amitriptyline), SSRIs, SNRIs, pregabalin and week opioids (tramadol). Table 5 presents the clinical practice guidelines.

Table 5: Current Clinical Practice Guidelines for Fibromyalgia

Management of Fibromyalgia Syndrome[54] (2004)	**Non-medicinal Therapies** Strong Evidence for Efficacy • Cardiovascular exercise: efficacy not maintained if exercise stops • CBT: improvement often sustained for months • Patient education: group format using lectures, written materials, demonstrations; improvement sustained for 3 to 12 months • Multidisciplinary therapy, such as exercise and CBT or education and exercise Moderate Evidence for Efficacy • Strength training, acupuncture, hypnotherapy, biofeedback, balneotherapy Weak Evidence for Efficacy • Chiropractic, manual, and massage therapy; electrotherapy, ultrasound. No Evidence for Efficacy • Tender (trigger) point injections, flexibility exercise **Medicinal Therapies** <u>Strong Evidence for Efficacy</u> • Amitriptyline: often helps sleep and overall well-being; dose, 25-50 mg at bedtime • Cyclobenzaprine: similar response and adverse effects; dose, 10-30mg at bedtime. <u>Modest Evidence for Efficacy</u> • Tramadol: long-term efficacy and tolerability unknown; administered with or without acetaminophen; dose, 200-300 mg/d • Serotonin reuptake inhibitors (SSRIs): Fluoxetine (only one carefully evaluated at this time): dose, 20-80 mg; may be used with tricyclic given at bedtime; uncontrolled report of efficacy using sertraline. • Dual-reuptake inhibitors (SNRIs): Venlafaxine: 1 RCT ineffective but 2 case reports found higher dose effective. • Milnacipran: effective in single • Duloxetine: effective in single • Pregabalin: second-generation anticonvulsant; effective in single <u>Weak Evidence for Efficacy</u> • Growth hormone: modest improvement in subset of patients with FMS with low growth hormone levels at baseline • Hydroxytryptamine (serotonin): methodological problems • Tropisetron: not commercially available • S-adenosyl-methionine: mixed results <u>No Evidence for Efficacy</u>

	• Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, melatonin, calcitonin, thyroid hormone, guaifenesin, dehydroepiandrosterone, magnesium
UpToDate[57] (2016)	Initial approach in every patient • Confirm the diagnosis • Education: explain the condition • Evaluate and treat comorbidities, such as mood and sleep disturbances Most patients • Trial with low-dose tricyclic antidepressants or selected antidepressants or anticonvulsants proven effective in fibromyalgia • Exercise program Patients not responding to above • Specialty referral (e.g., rheumatologist, physiatrist, psychiatrist, pain management) • Combinations of drug therapies • Physical therapy measures • Psychological interventions, such as cognitive behavioral therapy • Multidisciplinary programs
Management of chronic pain. A national clinical guideline[58] (Scotland, 2013)	Management of fibromyalgia pain • Duloxetine (60 mg/day) • Fluoxetine (20-80 mg/day) • Amitriptyline (25-125 mg/day)
Guidelines for the diagnosis and management of fibromyalgia syndrome: Executive summary[56] (Canadian, 2012)	Clinical Evaluation • Diffuse body pain for at last 3 months, waxes/wanes +/- fatigue, insomnia, cognitive changes, mood disorder, somatic symptoms otherwise unexplained. Physical examination should be normal except for point-tenderness by manual palpation (specific point tenderness examination is not required to confirm a diagnosis) o Laboratory testing: Erythrocyte sedimentation rate, C-reactive protein, creatinine kinase, thyroid stimulating hormone. Others as clinical evaluation suggests. Establish Diagnosis • Establish diagnosis early without need of specialist confirmation. American College of Rheumatology 2010 diagnostic criteria for fibromyalgia may be used. Remember symptoms vary over time, consider differential diagnosis and coexisting conditions acknowledging some medical/psychological conditions may mimic the presentation. Communicate this diagnosis to the patient. Team Approach • Generally, a primary care illness which may be augmented with multidisciplinary team approach involving specialist consultation (e.g. sleep, psychology) in patients failing primary care or with complex comorbidities Management • Strategy should include a multi-modal, self-management approach which is individualized, with regular monitoring and followup. Patients should identify specific goals for health/QOL. No pharmacological Treatments • Active patient participation: self-efficacy, social support, pursue a normal life pattern, with incremental activity/pacing increases to improve function • Psychological Interventions: Attainment of effective coping skills, promotion of self-management, evaluation/counseling for psychological distress (with encouragement to voice these issues), cognitive behavioural therapy • Physical Activity: graduated exercise program Complementary and alternative medicine

	• Evidence is insufficient, patients should be queried about use and provided information about efficacy and risks, where available.
	
	Pharmacological overview
	• Address most bothersome symptoms; attempt to address multiple symptoms with a single agent; consider drug interactions when combination therapy is required; initiate therapy with low doses; gradual titration may improve medication tolerance; regularly assess efficacy and side effect profile knowing drug side effects may mimic fibromyalgia symptoms; therapeutic modalities may be considered from a broad spectrum of categories
	
	Pain: Consistent with the WHO analgesic ladder
	• Consider acetaminophen with attention to daily dosage limits.
	• Nonsteroidal anti-inflammatory drugs should be used at the lowest dosage and shortest duration in view of potential serious adverse effects.
	• Opioids: for moderate to severe pain unresponsive to other treatment modalities, begin with a weak opioid (e.g. tramadol). Strong opioid use is discouraged. Continue only if pain and functional improvement are documented. Monitor for side effects, misuse.
	
	Nontraditional Pain Strategies
	• Pharmacological cannabinoid, especially in the setting of insomnia.
	• Antidepressants, addressing their use in pain vs psychological issues
	  ○ All antidepressants may be used for pain or other symptomatology: tricyclic antidepressants, selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors chosen by efficacy, physician knowledge, patient characteristics and side effect profile
	• Anticonvulsants, addressing their use as pain-modulators, beginning with the lowest dose, up-titration and attention to adverse events
	  ○ Health Canada approves only pregabalin and duloxetine for fibromyalgia management
	
	Additional recommendations concerning education and knowledge and patient follow-up
	• New symptoms require evaluation to evaluate the presence of a new medical illness
	• Long-term outcomes are favorable although symptomatology will fluctuate

EULAR evidence-based recommendations for the management of fibromyalgia syndrome[59] (European Union, 2008) **VA/DoD clinical practice guideline for the management of chronic multi-symptom illness[60] (2014)**	Understanding fibromyalgia: • Comprehensive assessment of pain, function, psychosocial context. • Complex, heterogeneous condition of abnormal pain processing with secondary features Treatment • Multidisciplinary approach including pharmacological and non-pharmacological modalities individualized for pain intensity, function, depression, fatigue, sleep etc. Non-pharmacological • Heated pool treatment +/- exercise, individualized exercise programs (aerobic and strength training), cognitive behavioral therapy, relaxation, rehabilitation, physiotherapy, psychological support Pharmacological • Pain: Tramadol, paracetamol other weak opioids. Not recommended: strong opioids or corticosteroids • Reduce pain and increase function: Antidepressants (amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindole) • Reduce pain and should be considered: Tropisetron, pramipexole and pregabalin Pain-Predominant Chronic Multi-Symptom Illness Weak for • Acupuncture, non-steroidal anti-inflammatory drug, tramadol (non-responsive to non-opioid or non-pharmacologic approaches), trial of selective norepinephrine reuptake

	inhibitor, tricyclic antidepressant, selective serotonin reuptake inhibitor or pregabalin. SNRI Fatigue-Predominant Chronic Multi-Symptom Illness Weak for • Acupuncture, of selective norepinephrine reuptake inhibitor, tricyclic antidepressant Weak against • Sleep pharmacotherapy • Stimulant medications Strong against • Antivirals, antibiotics • Corticosteroids • Immunotherapy
Pharmacological treatment of fibromyalgia syndrome Systematic review and meta-analysis (German, 2012) [61]	Recommended • Amitriptyline Recommended with comorbid depressive disorder or generalized anxiety disorder • Duloxetine (60 mg/day) Open recommendation with comorbid depressive disorder • Serotonin reuptake inhibitors (fluoxetine 20-40 mg/day, paroxetine 20-40 mg/day) Open Recommendation ("off-label" use) • Pregabalin (150 – 450 mg/day) No Positive or Negative Recommendation • Metamizole • Weak opioids (e.g. tramadol) • Acetaminophen Negative Recommendation • Cannabinoids • Flupirtine • Monoamine oxidase inhibitors • Muscle relaxants Strong Negative Recommendation • Anxiolytics • Dopamine agonists • Hormones (calcitonin, testosterone, estrogen, glucocorticoids, thyroid hormones, growth hormone) • Hypnotics • Ketamine • Local anesthetics • Milnacipran • Sodium oxybate • Neuroleptics • Nonsteroidal anti-rheumatics • Strong opioids • Serotonin receptor agonists (tropisetrone) • Virostatics

Abbreviations: CBT = cognitive behavioral therapy, RCT = randomized controlled trial, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin and norepinephrine reuptake inhibitor, EULAR = European League Against Rheumatism

Bipolar Disorder Disease Overview

Bipolar disorder (or manic-depressive disorder) is a mood disorder characterized by

episodes of depression and mania.[62] The prevalence of bipolar disorder is 0.4 to 1.4% across the world and 4% in the US.[30,63] In general, bipolar disorder occurs more frequently in women than men and the average age of first onset of the disease is 25 years. Bipolar disorder is the most expensive mental health disorder, with costs per affected individual doubling those of depression. The economic burden of bipolar disorder in the US results from indirect costs due to lost productivity resulting from absenteeism and presenteeism in addition to direct healthcare costs.[30] Bipolar disorder is also associated with an increased rate of substance abuse, legal and financial complications, relationship difficulties, self-harm and serious suicide attempts. Successful disease management and early treatment intervention can help to improve health outcomes and reduce the economic burden of bipolar disorders[30]

The depression-mania cycles associated with bipolar disorder are unpredictable. Manic episodes typically emerge over a period of days to weeks and persist up to several weeks or months. Mania is defined as a clearly elevated mood with unrestrained behaviors lasting at least a week with at least 3 symptoms, which may include irritability, grandiosity, sleeplessness, pressure talking, distractibility or engaging in activities with a high potential for adverse consequences. Clinical evidence suggests anger and agitation are the most common symptoms in pediatric patients while disordered thought content occurs most frequently in adult patients[64] In severe mania, symptoms similar to those seen in schizophrenia, including delusions and paranoid thinking, may present. The depressive episodes are defined as a persistent low mood including lack of positive affect and anhedonia causing impairment for greater than 2 weeks. In bipolar II disorder patients may lack the full criteria for mania and the recurrent depression episodes are instead separated by hypomania episodes with mild activation and increased energy.[3,62,65]

Treatment of bipolar disorder includes psychotherapy and medication therapy (mood stabilizers and antidepressant medications).[66,67] Mood stabilizers may include lithium, anticonvulsant therapies and antipsychotic agents. Lithium is typically the first-line agent and has demonstrated efficacy in the treatment of bipolar disorder with a response rate of 70-80%, beneficial effects within 1-2 weeks and prophylactic effects.[68-71] Antidepressants are effective in treating breakthrough depression episodes but may precipitate mania or accelerate cycle frequency. Recent clinical evidence suggests mood stabilizers demonstrating efficacy for mania are also efficacious for mixed episodes, reducing the need for antidepressant therapy.[72] Antipsychotic agents (such as aripiprazole, asenapine, cariprazine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone) may be used alone or in combination with other mood stabilizers or antidepressants to maintain mood stability, control agitation or treat bipolar disorder in patients experiencing loss of efficacy with lithium therapy.[3,72]

Clinical guidelines for the treatment of bipolar disorder include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Bipolar Disorder (2013)[73], the American Psychiatric Association Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)[66], the National Institute for Health and Clinical Excellence (NICE) Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014) [74] and American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007).[62] See

Table 6 for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment for acute manic and acute depressive episodes and maintenance therapy in patients at high risk for recurrence or severe disease. For selection of pharmacotherapy in the treatment of acute mania or depression episodes, factors to consider include: symptoms (such as euphoric, mixed, psychotic, suicidality), severity, treatment history, adverse effect profile and patient preference.[39,62,71,73]

Medication therapy for acute mania episodes (lithium, valproate, aripiprazole, risperidone, ziprasidone, etc.) should be continued until full remission.[62,75,76] If no response or only a partial response is achieved after 2 weeks of therapy, increase the dose of the medication or switch to another agent. Combination therapy is recommended in patients with continued treatment-resistance to a single agent. In patients with severe mania, clozapine or electroconvulsive therapy (ECT) may be indicated. Recommendations for antidepressant therapy in the treatment of acute depression episodes are inconsistent. In general, medication therapy for acute depressive episodes (antidepressants, lithium, quetiapine, olanzapine, lamotrigine, etc.) should be provided in an established treatment setting, in combination with behavioral therapy and regularly assessed for both efficacy and adverse effects. Before initiation of treatment for acute depression, all other potential medical causes should be ruled out and caffeine, alcohol and other substances should be discontinued. Of note, the full therapeutic effects of antidepressant therapy, lithium and lamotrigine may be delayed several weeks; short-term symptomatic treatment with benzodiazepines during the first few weeks of an acute bipolar episode may be required. Maintenance therapy is recommended in patients with three or more acute episodes, two acute episodes and a positive family history for bipolar disorder or in patients with severe disease.[62-64,67,70,71,73,75]

Table 6. Current Clinical Practice Guidelines for the Treatment of Bipolar Disorder

Guidelines	Recommendation
World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorder (2013)[73]	Treatment of an acute mania episode, any one of the following: • Aripiprazole 15-30 mg daily • Lithium 600-1200 mg daily (serum level 0.8-1.3 mmol, only if chronic treatment is being considered) • Risperidone 2-6 mg daily • Valproate 1200-3000 mg daily (loading dose 20-30 mg/kg; serum level 75-100 mg; not preferred in women of childbearing age) • Ziprasidone 80-160 mg daily Treatment of acute depressive episode: • Best evidence: quetiapine 300-600 mg daily • Good evidence: fluoxetine/olanzapine combination therapy • Fair evidence: bupropion, fluoxetine, imipramine, sertraline, in combination with a antimanic agent; lithium monotherapy; lithium in combination with lamotrigine tranylcypromine, venlafaxine Maintenance treatment, best evidence for: • Aripiprazole • Lamotrigine

	• Lithium • Quetiapine
National Institute for Health and Clinical Excellence (NICE) Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014)[39]	<u>Adults</u> Mania • Haloperidol, olanzapine, quetiapine or risperidone • Lithium alone or in combination with haloperidol, olanzapine, quetiapine or risperidone Depression • Fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine • Lithium alone or in combination with fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine Maintenance Therapy • Lithium alone or in combination valproate • Valproate, olanzapine, quetiapine <u>Precautions</u> There is an increased risk for side effects in young patients Antipsychotic treatment is not recommended for longer than 12 weeks in young patients For treatment of depression in young patients, a structured psychological intervention for at least 3 months is recommended Lithium and/or valproate should not be initiated in primary care Do not use lamotrigine for acute mania or mixed episode
American Psychiatric Association (APA): Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)[38]** ****"This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice"**	Acute manic or mixed episodes • Adjunctive antipsychotic therapy should be considered in manic or mixed manic episodes with psychotic features • Second-generation agents are recommended over first-generation agents due to side effect profile Acute depressive episodes • Adjunctive antipsychotic therapy or electroconvulsive therapy is recommended in acute depressive episodes with psychotic features Maintenance • Adjunctive antipsychotic therapy should be closely monitored, reassessed and slowly tapered, if indicated Acute rapid cycling • Combination therapy with a second-generation antipsychotic may be indicated
Veterans Affairs/Department of Defense (VA/DoD): Clinical Practice Guideline for	Mania: • Agents most likely to be beneficial include lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone; lithium or valproate may be combined with an atypical antipsychotic

Management of Bipolar Disorder in Adults (2010)[41]	Mixed episode • Agents most likely to be beneficial include valproate, carbamazepine, aripiprazole, olanzapine, risperidone or ziprasidone Depression • Agents most likely to be beneficial include quetiapine, lamotrigine, lithium, olanzapine/fluoxetine, olanzapine Treatment response should be evaluated at 4 to 8 weeks and periodically until full remission Patients who have failed monotherapy for mania: consider switching to another monotherapy or combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotic Treatment of severe mania or mixed episode: clozapine with valproate or lithium Treatment of severe depression: clozapine
The Texas Medication Algorithm Project (TMAP): Texas Implementation of Medication Algorithms (TIMA) Procedural Manual: Bipolar Disorder Algorithms (2007)[42]	Hypomania Or Mania <u>Stage 1</u> • Euphoric symptoms: lithium, valproate, aripiprazole, quetiapine, risperidone, ziprasidone • Mixed symptoms: valproate, aripiprazole, risperidone, ziprasidone <u>Stage 1b</u> • Olanzapine and carbamazepine are alternatives <u>Stage 2</u> • Combination therapy with two: lithium, valproate, olanzapine, quetiapine, risperidone, or ziprasidone (not 2 antipsychotics) <u>Stage 3</u> • A different combination than in Stage 2, with additional options: carbamazepine, oxcarbazepine, aripiprazole, a first-generation antipsychotic <u>Stage 4</u> • Clozapine or a 3-drug combination including lithium, an anticonvulsant mood stabilizer (valproate, carbamazepine, or oxcarbazepine) an atypical antipsychotic agent DEPRESSION <u>Stage 1</u> • Lamotrigine monotherapy for patients without a recent and/or severe history of mania OR lamotrigine plus a mood stabilizer <u>Stage 2</u> • Quetiapine monotherapy or olanzapine/fluoxetine combination treatment <u>Stage 3</u> • Evidence-based medicine is limited
American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with	Standard therapy (based on adult literature): lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated; antidepressants may be used as adjunctive therapy for bipolar depression The choice of medication should be based on • Evidence of efficacy • Illness phase • Presence of confounding symptoms

Bipolar Disorder (2007)[40]	• Side effects • Patient's medication response history • Patient and family preferences Clozapine or electroconvulsive therapy are reserved for treatment-refractory cases Maintenance medication therapy may be recommended to prevent relapse Baseline and follow-up review of symptoms/efficacy, adverse effects and laboratory monitoring is recommended Trial of 6 to 8-week with a mood-stabilizing agent is recommended before switching agents or adding an additional agent Psychotherapy is recommended as part of a comprehensive treatment plan

Vasomotor Symptoms of Menopause

Paroxetine mesylate is the only SSRI/SNRI agent indicated for treatment of vasomotor symptoms associated with menopause. Menopause is associated with irregular menstrual cycles and hormone fluctuations producing vasomotor symptoms and changes in sleep.[77-79] Sexual function, vaginal atrophy, vaginal dryness, dyspareunia, cognitive and mood changes and sexual dysfunction are common symptoms. Changes in the concentration of follicle-stimulating hormone and estradiol are associated with the symptoms of menopause. Vasomotor symptoms and hot flashes are the most troublesome symptoms.[77] Diagnosis is made upon irregular or absent menstrual cycles in women over 45 years. Up to 80% of women experience vasomotor symptoms (hot flashes) during the transition to menopause. Although hot flashes subside naturally in most women, up to 9% will have symptoms persist into their 70's, although only 1/4 will seek treatment.[77] Symptoms begin suddenly, with feelings of heat in the chest and face, profuse sweating and often palpitations. The sensation subsides over a few minutes and may be followed by anxiety and chills. Sleep is often disturbed by vasomotor symptoms at night.[77,79,80] The number of hot flashes varies greatly among women. Keeping cool may be the only intervention needed for many women. When symptoms are significant and in the absence of a history of breast cancer or cardiovascular risk, treatment usually includes the use of low-dose estrogen/progestin therapy for women with a uterus and low-dose estrogen for women post-hysterectomy. The alternatives to hormone therapy are selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, clonidine or if nighttime symptoms are most troubling, pregabalin or gabapentin. The use of antidepressants may be a first choice in women with concomitant mood disorders. The use of over-the-counter products have not been proven safe or effective and are not recommended. Women taking tamoxifen should not receive fluoxetine or paroxetine. Symptoms usually cease on average after two years and treatment discontinuation should be considered periodically.[77-79]

Clinical practice guidelines include the Endocrine Society of the US[81], NICE Women's and Children's Health Collaborative[82], the American College of Obstetrics and Gynecologists[83] and the Menopause and Osteoporosis Working Group[79]. See Table 5 for a summary of the most current guideline recommendations. After screening for history or risk of breast cancer or cardiovascular illness, first-line therapy consists of hormone replacement therapy, using the lowest hormone doses for the shortest periods of time. Alternatives include serotonin reuptake

inhibitors and serotonin/norepinephrine reuptake inhibitors, gabapentin, pregabalin and clonidine. Most groups do not endorse the use of alternative or complementary therapies. Table 7 presents the clinical practice guidelines.

Table 7: Current Clinical Practice Guidelines for the Treatment of Menopause

Menopause: Diagnosis and Management National Collaborating Centre for Women's and Children's Health. Menopause: diagnosis and management. London (UK): National Institute for Health and Care Excellence (NG23)(2015)[82]	Women with or at high risk of breast cancer
	• The SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen
	Vasomotor Symptoms
	• Offer hormone replacement therapy
	  ○ Discuss short and longer-term benefits and risks
	  ○ Oestrogen and progestogen to women with a uterus
	  ○ Oestrogen alone to women without a uterus
	• Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone.
	• Isoflavones/black cohosh may relieve vasomotor symptoms
	  ○ Safety of the various preparations is uncertain
	  ○ Preparations may vary
	  ○ Drug interactions have been reported
	Psychological Symptoms
	• Evidence is insufficient to support the use of SSRIs or SNRIs to ease low mood in menopause in the absence of a diagnosis of depression

Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline, (2015)[81]	Non-hormonal therapies for vasomotor symptoms
	• Mild symptoms to less bothersome hot flashes
	  ○ Lifestyle changes: Turn down the thermostat, dress in layers, avoid alcohol and spicy foods, reduce obesity and stress
	• Moderate to severe symptoms where hormone therapy is contraindicated or not desired and there are no contraindications to prescription therapies
	  ○ Selective serotonin reuptake inhibitors
	  ○ Selective serotonin-norepinephrine reuptake inhibitor
	  ○ Gabapentin
	  ○ Pregabalin
	• Moderate to severe symptoms not responding to non-hormonal prescription therapies and there are no contraindications
	  ○ Clonidine
	• Over-the-Counter and alternative therapies
	Lack of consistent evidence for botanicals, black cohosh, omega-3-fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis

Management of menopausal symptoms: American College of Obstetricians and Gynecologists (ACOG) (2014)[83]	Vasomotor Symptoms • Systemic hormone therapy with estrogen +/- progestin is most effective

	○ Low- and ultra-low dose systemic estrogen therapy has a better adverse event profile and may be effective in some women. ○ Individualize care using the lowest effective dose for the shortest duration of time ○ Combined systemic hormone therapy risks include thromboembolic disease and breast cancer. • Effective alternatives to hormone replacement therapy ○ Selective serotonin reuptake inhibitors (SSRIs) • Paroxetine mesylate (Brisdelle®) is the only non-hormonal therapy approved by the FDA ○ Selective serotonin norepinephrine reuptake inhibitors (SNRIs) ○ Clonidine • Reasonable measures, include layered clothing, lowering ambient temperature, consuming cool drinks • There is inconsistent evidence and no recommendation is made for progestin-only medications, testosterone, or compounded bioidentical hormones, phytoestrogens, herbal supplements, and lifestyle modifications.
Managing menopause: Menopause and Osteoporosis Working Group (2014) [79]	Vasomotor Symptoms • Menopausal transition period: Progestins alone or low-dose oral contraceptives • Mild vasomotor symptoms ○ Lifestyle modifications – reduce core body temperature, exercise, weight management, smoking cessation, avoidance of triggers (e.g. hot drinks, alcohol) • Active vasomotor symptoms ○ Hormone therapy: estrogen +/- progestin is most effective ○ Non-hormonal prescription therapies are associated with side effects but may be considered when hormone therapy is contraindicated or not desired. ▪ Antidepressant ▪ Gabapentin ▪ Clonidine • Due to limited evidence of benefit and minimal safety data do not recommend complementary or alternative therapy approaches.

Premenstrual Dysphoric Disorder

Fluoxetine, paroxetine and sertraline are labeled for use in the treatment of premenstrual dysphoric disorder. Physical, mood and behavioral changes associated with the menstrual cycle exist on a continuum from mild discomfort to incapacitating symptoms.[78,84] Premenstrual syndrome is diagnosed by the presence of 1 symptom within 5 days of menstruation that subsides upon menstruation and remains quiescent through the follicular phase. Premenstrual dysmorphic syndrome is a more severe presentation with somatic, emotional and behavioral symptoms that impair daily living.[85] Diagnosis requires the presence of 5 of 11 symptoms present for at least 2 consecutive months or cyclically for over 1 year, including depressed mood

or dysphoria, anxiety/tension, affective lability or irritability. Other symptoms for diagnosis include anhedonia, difficulty concentrating, lack of energy, changes in eating or sleep, or feeling overwhelmed. Physical findings include breast tenderness or bloating. Symptoms must interfere with normal living (work, school, usual activities, relationships) and not represent another disorder.[84] Many of the symptoms are common to other psychiatric mood and anxiety disorders, which have been associated with serotonergic (5HT) dysfunction. Animal studies reveal that ovarian steroid function affects central serotonin function. Hypothalamic diurnal fluctuations in $5HT_{26}$ are induced by estrogen while progesterone increases $5HT_{27}$ turnover. Some investigators have shown abnormal 5HT activity in premenopausal dysmorphic women by growth hormone, cortisol or prolactin response studies. Since serotonin activity is inversely related with activity of the hypothalamic-pituitary axis, the use of serotonin reuptake inhibitors may reverse irritability, mood changes, dysphoria, reduce physical symptoms and improve psychosocial functioning.[84]

Treatment involves lifestyle modifications (exercise, reducing caffeine, chocolate, tobacco, alcohol and sodium intake, increasing small complex carbohydrate rich meals, dietary supplementation with vitamin B6 and calcium), psychosocial interventions (peer support, cognitive behavioral therapy, and relaxation and stress management techniques) and pharmacologic interventions. Maintaining patient diaries is helpful in identifying triggers.[78,84]

Non-pharmacologic interventions include cognitive behavioral therapy and reflexology. Low-level pharmacological interventions include calcium carbonate (1-1.2 gm/day), magnesium (200-360 mg during luteal phase) and pyridoxine (100 mg/day). Limited data suggests a benefit may be obtained with mefenamic acid, naproxen, spironolactone or bromocriptine for specific symptoms. Good evidence supports the use of all selective serotonin reuptake inhibitors, clomipramine and L-tryptophan. Serotonin reuptake inhibitors may be dosed continuously, intermittently, or semi-intermittently. Continuous therapy involves daily dosing throughout the menstrual cycle. Intermittent dosing begins around ovulation and continues through day 1 or 2 of menstruation. Semi-intermittent dosing involves the continuous administration of a low dose of medication supplemented with higher doses during the luteal phase.[84] Evidence suggests anxiolytics are efficacious but less so than selective serotonin receptor inhibitors and carry increased risks of side effects and dependence. Second-line treatments include hormonal therapies (gonadotropin-releasing hormone, low-dose estrogen and progesterone, intranasal buserelin, and intramuscular leuprolide and danazol. Severe cases may be treated surgically via ovariectomy.[84]

Clinical guidelines for the treatment of premenstrual dysphoric disorder include expert recommendations from the Association of Reproductive Health Professionals[86] and from the Psychiatry and Behavioural Neurosciences, and Obstetrics and Gynecology groups of McMaster University. [87] Lifestyle changes are recommended for mild symptoms of premenstrual syndrome. As the severity of symptoms increases, recommendations include over-the-counter supplements, non-prescription medications and finally serotonergic antidepressants are the first-line pharmacologic therapy. Additional therapies include venlafaxine, clomipramine, anxiolytics and hormonal therapy. Some data supports the use of bromocriptine, spironolactone and drosperinone for specific symptoms. Table 8 presents a summary of the guideline recommendations.

Table 8: Clinical Practice Guidelines for the Treatment of Premenstrual Dysphoric Disorder

Guideline	Recommendation
Managing Premenstrual Symptoms (2008)[86]	Lifestyle Changes • Eat frequent, small portion, high complex carbohydrate foods • Reduce salt, sugar, caffeine, dairy products and alcohol • Consider supplementation with Vit B6 (up to 100 mg daily), Vitamin E (up to 600 IU daily), Calcium (1200mg & Vit D 400 IU daily in divided doses), Magnesium (up to 500 mg daily), Chaste tree extract (*Vitex agnus-castus)* 30-40 mg daily • Behavioral counseling, aerobic exercise, yoga, relaxation and stress management, anger management, self-help and support groups, cognitive and/or individual/couples-therapy, smoking cessation, regular sleep, light therapy • Trial the above for 2-3 month Nonprescription Medications • Non-steroidal anti-inflammatory medications (NSAIDs) Pharmacologic Treatment First-Line: Selective serotonin reuptake inhibitors Fluoxetine 20 mg daily Sertraline 50-150 mg daily Paroxetine 10-30 mg daily Citalopram 5-20 mg daily Fluvoxamine 50-100 mg daily Others: Venlafaxine XR 75-112.5 mg daily Clomipramine 25-75 mg daily Level 1: Mild to moderate premenstrual syndrome • Lifestyle, non-prescription drugs, relaxation therapy, cognitive behavioral therapy Level 2: Premenstrual syndrome with physical problems predominating • Spironolactone 25 mg daily for breast tenderness and bloating • Oral contraceptives (regular or long cycle) or medroxyprogesterone acetate for breast and abdominal pain • NSAIDs during the luteal phase Level 3: Premenstrual syndrome or premenstrual dysphoric disorder with mood symptoms predominating • Selective serotonin reuptake inhibitor (SSRI) on symptom days only ○ Try at least 3 different SSRIs (including venlafaxine) • Continuous SSRIs ○ Try at least 3 different SSRIs (including venlafaxine) • Buspirone during the luteal phase

	Level 4: Premenstrual dysphoric disorder not responsive to therapy for levels 1-3 • Continuous high-dose progestin daily (oral medroxyprogesterone 20-30 mg daily, depo-medroxyprogesterone acetate 150 mg every 3 months) • Gonadotropin releasing hormone (GnRH) at the usual dose with add-back estrogen/progestin if continued beyond 6 months
Expert guidelines for the treatment of severe PMS, PMDD, and comorbities: The role of SSRIs (2006) [87]	Lifestyle Modification • Exercise, reducing caffeine, increasing complex carbohydrates, supplements (calcium 600 mg twice daily, vitamin B6 50-100 mg daily, chasteberry) Psychosocial Interventions • Peer support, cognitive-behavioral modifications, relaxation training, stress management techniques Pharmacological Therapies First-Line: Serotonergic antidepressants • Serotonin reuptake inhibitors, clomipramine, venlafaxine Other • Anxiolytics (alprazolam, buspirone) • Hormonal interventions (gonadotropin-releasing hormone, oral contraceptives, danazol) Symptom Specific Therapies • Breast tenderness: Bromocriptine • Bloating and weight gain: Spironolactone • Food cravings, appetite, acne: Drosperinone

Post-Traumatic Stress Disorder (PTSD)

Post-Traumatic Stress Disorder (PTSD) is a psychobiologic, anxiety disorder typically resulting from exposure to a trauma. Symptoms may occur acutely or may be delayed in onset up to 6 months in some patients.[88] PTSD is associated with a triad of symptoms, including 1) psychic numbing, denial or avoidance; 2) re-experiencing the traumatic event, intrusion or flashbacks; and 3) hyperarousal symptoms in the presence of distress, difficulty or impairment in daily functioning.[88-90] Acute PTSD is defined as lasting 1-3 months following exposure to trauma while chronic PTSD continues beyond 6 months.[89] PTSD often presents with sleep disturbances, mood disorders, pain, somatization, substance abuse, depression, anxiety, interpersonal relationship problems and identity issues.[88] Up to 70% of adults in the US have experienced a traumatic event. Twenty percent will go on to develop PTSD and at any given time, 8% of adults in the US have PTSD. Women are twice as likely to be diagnosed with PTSD than men. From 2012-2013, the number of PTSD cases diagnosed in military persons increased by 50%. In men, the presentation relates to combat exposure and in women to sexual assault. People with PTSD are the greatest utilizers of health care, associated with a societal cost of $42.3 billion.[91] Prevention and treatment of PTSD may include behavioral therapies and medications. Early identification and treatment may limit functional impairment although the prognosis is overall

poor with up to 1/3 of persons not recovering.[92] Currently, no pharmacotherapy has shown effectiveness in preventing PTSD. Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacotherapy for PTSD. SSRIs are relatively safe medications with few adverse effects; are effective in reducing the triad of symptoms; are effective therapies for commonly associated comorbid psychiatric disorders (e.g. panic, depression, social phobia and obsessive-compulsive disorder), complicating clinical symptoms (e.g. suicidality, impulsivity, aggressive behavior) and are effective in both men and women. Other antidepressants, including tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), may be beneficial in the treatment of PTSD. Treatment with fluoxetine, sertraline and paroxetine reduced anger and irritability symptoms within one week and the triad of symptoms over 2 to 4 weeks. The choice of specific agent should be based upon the pharmacokinetics, adverse events, interactions, metabolic effects, etc. Benzodiazepines may be used adjunctively for anxiety and sleep, although dependence and worsening symptoms upon discontinuation have been reported. Other medications with limited evidence supporting their use include second-generation antipsychotics, anticonvulsants, alpha-2 agonists and beta adrenergic blockers [88] Table 9 summarizes the current clinical practice guidelines for PTSD.

Table 9: Clinical Practice Guidelines for Treatment of PTSD

Australian guidelines for the treatment of acute stress disorder & posttraumatic stress disorder. Melbourne (Australia): Australian Centre for Posttraumatic Mental Health (2013)[93]	Early Pharmacological Interventions for Adults
	• Medications should not be use preventively
	• Sleep medications (time-limited) may be used if sleep hygiene, psychological interventions are not effective.
	• Routine use of pharmacotherapy within 4 weeks of symptom onset is not recommended
	• Pharmacotherapy is indicated when distress is not managed by psychological means and a pattern of extreme hyperarousal, sleep disturbance or nightmares is present.
	• Consider medications if patients with a prior psychiatric history responsive to medications exhibit persistent intrusions with affective distress
	Pharmacologic Interventions
	• First-line treatment remains trauma-focused cognitive behavioral therapy or eye movement desensitization and reprocessing.
	• First-line medications
	  ○ Selective serotonin reuptake inhibitor antidepressants (SSRIs)
	  ▪ Person unwilling or unable to engage psychological treatment
	  ▪ Presence of concomitant condition for which SSRIs are indicated (e.g. severe depression with dissociation)
	  ▪ Circumstances are unstable not supporting psychological treatment (e.g. ongoing domestic violence)
	  ▪ Psychological, trauma-focus treatment has not been successful
	• Inadequate response to pharmacotherapy
	  ○ Consult a specialist
	  ▪ Increase current dose of medication
	  ▪ Switch to alternative antidepressant medication
	  ▪ Add prazosin, risperidone or olanzapine, adjunctively
	  ▪ Reconsider psychological intervention

	• Continue therapy for 12 months with gradual withdrawal if responsive to treatment without significant adverse effects

VA/DoD Clinical practice guideline for management of post-traumatic stress: The Management of PTSD Working Group (2010)[94]	Early PTSD
	• No evidence supports early pharmacotherapy to prevent the development of PTSD
	  ○ Benzodiazepines are specifically noted to be of no benefit
	<u>First-line</u> treatment options include pharmacotherapy and psychological therapy
	• SSRI or SNRI reassess response at 2-4 weeks. Switch to alternate if not tolerated
	  ○ Some benefit with
	  ▪ Mirtazapine
	  ▪ Prazosin (for sleep/nightmares)
	  ▪ Tricyclic antidepressants (TCAs)
	  ▪ Nefazodone
	  ▪ Monoamine oxidase inhibitors (MAOIs)(phenylzine)
	  ○ Unknown benefit with
	  ▪ Atypical antipsychotic (except risperidone, as adjunct)
	  ▪ Atypical antipsychotic (monotherapy)
	  ▪ Conventional antipsychotics
	  ▪ Buspirone
	  ▪ Non-benzodiazepine hypnotics
	  ▪ Bupropion
	  ▪ Trazodone(adjunctive)
	  ▪ Gabapentin
	  ▪ Lamotrigine
	  ▪ Propranolol
	  ▪ Clonidine
	  ○ No benefit with
	  ▪ Benzodiazepines
	  ▪ Tiagabine
	  ▪ Guanfacine
	  ▪ Valproate
	  ▪ Topiramate
	  ▪ Risperidone
	• No response to initial therapy
	  ○ Assess adherence
	  ○ Increase dose
	  ○ Consider longer duration
	  ○ Switch to alternate SSRI or SNRI
	  ○ Add psychotherapy
	  ○ Consider specialist referral
	• Fail second attempt at pharmacotherapy
	  ○ Switch to alternate SSRI or SNRI or mirtazapine
	  ○ Add psychotherapy
	  ○ Augment with prazosin (sleep/nightmares)

<u>Generalized Anxiety Disorders</u>

Anxiety disorders are the most common outpatient psychiatric illnesses.[44] Anxiety is a sense of dread, unease or foreboding that may be associated with a number of medical conditions.[7,95] The diagnosis of a general anxiety disorder involves excluding

other precipitants, comorbid conditions or diagnoses that may be the primary cause of anxiety. Up to 75% of patients having panic attacks will meet the diagnosis for a major depressive disorder. Many patients have alcohol or substance abuse problems that originated from attempts at self-medicating. Anxiety disorders are classified by the precipitant, duration and course of anxiety.[7,96]

Generalized Anxiety Disorder (GAD)

Generalized anxiety disorder (GAD) manifests with worry that is persistent, excessive and often unrealistic.[7,97] Physical complaints include muscle tension an inability to concentrate and arousal symptoms (e.g. restlessness and insomnia) commonly. Diagnosis is made when excessive worry and anxiety are difficult to control, continue for 6 months on more than half the days and is associated with a number of psychological and physical findings.[96] The diagnosis is most commonly made before age 20 in people who grew up with childhood fears. There may be a genetic component as the illness is common in people with first-degree relatives with the illness. Psychiatric comorbidities are common, including major depression, dysthymia or social phobia. Patients often self-medicate with alcohol or sedative/hypnotics.[44,95,98,99]

Treatment involves a combination of psychotherapy and pharmacotherapy.[7,95,97-102] Therapy is often initiated with a short course of a benzodiazepine. Lorazepam, oxazepam and alprazolam are preferred due to low hepatic metabolism and lack of active metabolites. Medications are initiated at the lowest dose and used only as-needed. The more rapidly absorbed agents have the most rapid onset of action but also the greatest abuse/dependence potential. Longer acting agents may accumulate resulting in sedation, cognitive impairment and psychomotor retardation while short acting agents may produce anxiety, insomnia and more rebound effects upon discontinuation. Benzodiazepine therapy should be discontinued by a slow taper. Transitioning patients from long-acting to short-acting agents may allow more flexibility and aid in discontinuing therapy. Adjunctive carbamazepine or beta-blockers may be useful in the discontinuation process. Buspirone is an anxiolytic, which may be effective in the treatment of generalized anxiety disorders but requires multiple daily doses and several weeks before a response is seen. The SSRI/SNRI agents escitalopram, paroxetine, venlafaxine and duloxetine (a dual-acting antidepressant) are labeled for use in GAD at typical antidepressant doses and may be safer for long-term treatment of chronic anxiety. Other agents that may be effective include the GABAnergic acting anticonvulsants, divalproex, gabapentin, oxcarbazepine, pregabalin and tiagabine.

Panic Disorder

Panic disorders are unpredictable episodes of fear associated with a sense of impending doom and physical manifestations (e.g. palpitations, sweating, shortness of breath, chest pain, dizziness). Symptoms heighten over 10 minutes and subside within an hour. A diagnosis of a panic disorder requires a one-month history of changes in behavior, and worry or concern due to the panic attack. This disorder usually manifests in late adolescence. The goal of therapy is to reduce the number, duration and intensity of attacks. Psychotherapeutic interventions should be instituted upon diagnosis. Symptoms may be reduced by 75% although not eradicated. Treatment with selective serotonin

reuptake inhibitors (SSRIs) is associated with fewer side effects than with tricyclic antidepressants. SSRI therapy is initiated at low doses, 1/3 to 1/2 the antidepressant dose. Patients with atypical depression may benefit from treatment with a monoamine oxidase inhibitor. A clinical response may be delayed up to 6 weeks. Antidepressant doses should be titrated upward as required. Often patients are given short courses of anxiolytics (benzodiazepines) to reduce symptoms until the antidepressant medication becomes effective.

Social Anxiety Disorder (SAD)

SAD begins with persistent fear of other people in settings in which their behavior or performance may be judged or when strangers are present. The irrationality of the fear is understood but the person remains anxious and unable to function. SAD produces an anxiety reaction, which may result in panic attacks, leading to avoidance behaviors that impact social and occupational functioning. Females are more commonly affected. Symptoms often date to early childhood with diagnosis by early adulthood. First-line treatment includes cognitive behavior therapy CBT. Patients unwilling to participate in CBT may be started on SSRIs. Psychodynamic therapy may be useful in patients who decline CBT or drug therapy. Combination CBT/pharmacotherapy is recommended in patients who do not respond to their initial therapy. The use of serotonin/norepinephrine reuptake inhibitors or monoamine oxidase inhibitors may be tried after first-line therapies fail or produce only a partial response.

Clinical guidelines for the treatment of anxiety disorders include two National Institute for Health and Care Excellence (NICE) guidelines, one addressing the management of generalize anxiety and panic disorders in adults[95] and a second developed by the National Collaborating Centre for Mental Health on behalf of NICE addressing social anxiety disorder.[100] Table 10 presents the clinical practice guidelines.

Table 10: Current Clinical Practice Guideline for Drug Treatment of Anxiety Disorders

NICE: Generalized anxiety disorder and panic disorder in adults: management. [CG113][95]	Step 1: Identify and assess, educate about generalized anxiety disorder (GAD) and treatment options; active monitoring
	
	Step 2: Psychological interventions, self-help, individual guided self-help, psychoeducational groups
	
	Step 3: Choice of high-intensity psychological intervention (cognitive behavior therapy (CBT) or applied relaxation or drug treatment
	
	Psychological Intervention: 12 to 15 1-hour sessions of psychological intervention
	
	Pharmacological Treatment:
	
	First-line: Selective serotonin reuptake inhibitor (SSRI): Most cost effective; obtain informed consent; monitor adverse effects and response
	
	• If ineffective, a trial of a second SSRI or a serotonin/norepinephrine reuptake inhibitor (SNRI), considering:
	  ○ Withdrawal syndrome with paroxetine, venlafaxine
	  ○ Side-effect and drug interaction profile

	○ Risk of suicide, toxicity in overdose (venlafaxine) ○ Prior treatment history (adherence, side effects, withdrawal syndrome, patient preference) • If unable to tolerate SSRI/SNRI, consider pregabalin • No NOT use benzodiazepine except short-term in primary or secondary care • Do NOT use antipsychotics for GAD in primary care • Prior to therapy discuss with the patient – benefits of treatment, drug propensities for side effects, withdrawal reactions, drug interactions, risk of activation symptoms, full anxiolytic effect requiring 1 week or more, importance of adherence/compliance • Consider bleeding risk with SSRIs especially in older people, those taking agents that can damage the gastrointestinal mucosa or interfere with clotting: Consider prescribing a gastroprotective agent • Patients under 30 years: Warn concerning the increased risk of suicidal thoughts and self-harm AND see them in 1 week AND monitor for the first month. • Side effects: Developing soon after initiation of treatment ○ Monitor closely for mild symptoms, reduce the dose or stop the drug and initiate an alternative medication or initiate high-intensity psychological intervention • Review effectiveness, side effects every 2-4 weeks for 3 months then every 3 months. • If effective, continue therapy at least one year (relapse rate is high) IF Step 3 is inadequate: Offer alternative treatment (psychological or pharmaceutical); offer intensive psychological intervention for partial-medication responders or refer to Step 4 if risk of self-harm, suicide, significant comorbidity or self-neglect or inadequate response to Step 3 options. Step 4: Complex drug and/or psychological treatment regimens; input from multi-agency teams, crisis services, day hospitals, inpatient care. • Specialist assessment, review patient, family, carers needs, develop a comprehensive care plan. • Treatment: Offer interventions they have not tried ○ Consider combining psychological and drug treatments ○ Combinations of antidepressants ○ Augmentation of antidepressants ▪ Caution that effectiveness of combination treatments is lacking ▪ Side effects, drug interactions are more likely
NICE: Social anxiety disorder: recognition, assessment and treatment NICE guidelines [CG159], 2013[96]	Interventions for Adults • Cognitive behavioral therapy (CBT), not group therapy or CBT-based supported self-help. Promote CBT before pharmacological therapy • IF the person wished pharmacologic therapy offer selective serotonin reuptake inhibitor (SSRI) such as escitalopram or sertraline. Monitor for adverse reactions

	• IF patients decline both CBT and drug therapy consider psychodynamic therapy
	For Partial Response to CBT
	• Consider combination of drug therapy and CBT
	For Partial Response to Drug Therapy (after 12 weeks) or Side Effects
	• Alternative SSRI (fluvoxamine or paroxetine) or serotonin/norepinephrine reuptake inhibitor (SNRI), such as venlafaxine, considering:
	  ○ Paroxetine and venlafaxine produce a discontinuation syndrome (extended with ER preparations), risk of suicide and toxicity in overdose
	For non-response to SSRI/SNRI
	• Consider monoamine oxidase inhibitor (MAOI) such as phenylzine or moclobemide
	• Discuss individual CBT
	Interventions for Children and Young People
	• Individual or group CBT (may involve parents or carers)
	• NOT recommended
	  ○ Pharmacological interventions, including anticonvulsants, tricyclic antidepressants, benzodiazepines, or antipsychotic medication, St. John's wort or other over-the-counter preparations, botulinum toxin for hyperhidrosis

Key: GAD=generalized anxiety disorder, SSRI=selective serotonin reuptake inhibitor, SNRI=selective serotonin/norepinephrine reuptake inhibitor, CBT=cognitive behavior therapy

Pharmacology

The monoamine hypothesis, a theory about the etiology of depression that has persisted for decades, has been challenged recently. It was developed in the 1950's from the observation that symptoms of depression were reduced in patients receiving iproniazid or imipramine, prompting pursuit of a common, single pathway. Iproniazid inhibits enzymatic monoamine breakdown. Imipramine blocks both the serotonin reuptake transporter (SERT) and norepinephrine transporter (NET) resulting in increased synaptic neurotransmitter levels. Reserpine was shown to reduce monoamine levels and produced symptoms of depression. Developed over 30 years ago, the monoamine hypothesis proposed that symptoms of depression resulted from a depletion of serotonin, norepinephrine and/or dopamine in the brain.[103] The monoamine theory posits that medications that increase presynaptic monoamine release or block reuptake will yield higher synaptic concentrations of amines, a reduction in depressive symptoms and elevated mood. Selective serotonin reuptake inhibitors block the SERT reuptake pump by 60-80%. The delay in clinical response to treatment with antidepressants is explained as a genomic response occurring over several weeks which downregulates the inhibitory $5HT_{1A}$ receptors, allowing for greater neuronal firing and greater serotonin release.[7,104-106]

There are a number of problems with monoamine hypothesis of depression:[102,104,107-108]

1. Animal models of stressors that trigger depression consistently find elevated brain serotonin levels.
2. Cocaine and amphetamine block serotonin reuptake but are ineffective in treating depression.
3. Tianeptine is an effective antidepressant even though it increases serotonin reuptake and reduces intra-synaptic serotonin levels.
4. Current data suggests reserpine may actually be useful to treat depression.
5. Reductions in serotonin synthesis by depletion of the precursor, tryptophan, do not result in depression.
6. Administration of ketamine, a glutamate receptor blocker results in rapid antidepressant effects (unlike the serotonergic antidepressants) suggesting changes in serotonin occur distal to the actual physiologic process associated with depression.
7. Genetic differences have been identified, specifically polymorphism of the SERT gene. People with the short s-allele have reduced transporter mRNA densities and reduced serotonin synaptic clearance. This genetic SERT downregulation results in higher intra-synaptic serotonin levels than normal people, but is associated with a higher incidence of depressive symptoms especially following stress.
8. Serotonin levels are high in a number of depressive phenotypes including melancholia, infection and starvation.
9. Selective serotonin-reuptake inhibitors produce both increases and decreases in anxiety, anhedonia and motor activity. A single dose of citalopram increases anxiety while chronic use reduces it. Social anxiety is considered a state of serotonin excess. People with social anxiety often have comorbid depression (36-58%) and those with depression often have comorbid social anxiety (20-45%).
10. Acute use of an antidepressant medication worsens symptoms, yet continued use improves symptoms while chronic use results in a return to baseline symptoms. Fluoxetine use is associated with a relapse rate of 46% at 12 months. Relapse rates average 60% over two years with use of any antidepressant medication.
11. Depressed people crave carbohydrates. Carbohydrate consumption increases the concentration of the serotonin precursor, tryptophan, in the brain. Instead of improving symptoms of depression secondary to increased serotonin production, carbohydrate consumption is associated with increased depressive symptoms while studies demonstrate that decreasing caffeine and carbohydrate intake improve symptoms.
12. The best measure of serotonin transmission in humans is jugular vein 5-hydroxyindoleacetic acid (5HIAA) levels which are higher in depressed than non-depressed persons, average 2.4-fold higher in depressed patients with the s-allele, and decline over 12 weeks with SSRI therapy.
13. Post-mortem studies of the brain of depressed patients have not documented reduced levels of brain norepinephrine or serotonin.
14. Long-term administration of antidepressants results in a downregulation of amine receptors.
15. Brain derived neurotrophic factor (BDNF) levels are reduced in the brains of depressed patients.
16. Concentrations of neurotransmitters increase hours after administration of antidepressants although the clinical effects are delayed by weeks.
17. Meta-analysis of antidepressant medications demonstrate only modest benefit over placebo in the treatment of depression.

It is currently believed that secondary receptor and cellular compensatory mechanisms play an important role in the mechanism of action of selective serotonin and selective serotonin/ norepinephrine reuptake inhibitors. A number of newer hypothesis are being explored. It is likely that the full mechanism will incorporate at least parts of the various theories.[6] The high-serotonin theory of depression proposes the serotonin system is involved in energy regulation, coordinating metabolic processes with storage, mobilization, distribution, production and utilization of energetic resources to meet adaptive demands. This theory has energy homeostasis vs. serotonin homeostasis at its core. Administration of serotonergic antidepressants result in an overall increase in brain serotonin with a shift in the extracellular to intracellular ratio. The increase in serotonin levels and disruption of the extracellular/intracellular ratio associated with the SSRI/SNRI agents is believed to disrupt energy homeostasis resulting in worsening symptoms. Increased serotonin levels increase glutamatergic, glycolytic, oxidative phosphorylation and inhibit glucose consumption in the brain. Over time, the $5HT_{1A}$ receptor is tonically activated as a postsynaptic, compensatory mechanism inhibiting the effects of serotonin on glutaminergic activity. Homeostasis is restored over a number of weeks. As serotonin levels decline, depressive symptoms improve. The brain compensatory changes require weeks to occur and result over time in a return to baseline serotonin levels suggesting the mechanism for the high rate of long-term antidepressant treatment failure.

The neurotrophic hypothesis of depression states that depression is associated with dysfunctional, histologic changes in the brain resulting from stress. Stress-induced neurohistologic changes in the amygdala, hippocampus and prefrontal cortex are thought to produce the cognitive, behavioral and affective impairments seen in depression. This hypothesis presents depression not as a chemical imbalance, but rather a disorder of the hardwiring of the brain. Studies demonstrate that reductions of brain derived neurotropic factor (BNDF) levels in the hippocampus associated with stress/depression can be restored by antidepressant therapy which increase various forms of neuronal plasticity, including BNDF and brain-specific cytoplasmic RNA (Bc1-2) activity to improve mood.[108,109] BNDF levels initially decline upon antidepressant therapy but increase with continued administration, accounting for the delay in therapeutic response.[105,109-111]

SSRIs are active at the serotonin receptor whiles SNRIs are active at both the serotonin and norepinephrine transporter sites and are considered dual-acting. SSRIs and SNRIs vary in their affinity for the transporters. Although considered dual-acting, the SNRIs also increase prefrontal cortex dopamine concentrations via norepinephrine transporters.[112]

Citalopram is a mix of (S) and (R) stereoisomers. Escitalopram is the s-stereoisomer of citalopram, which is the more potent inhibitor of serotonin reuptake. Structurally, paroxetine and fluvoxamine are unrelated to other SSRIs. Paroxetine weakly binds to cholinergic receptors accounting for more anticholinergic side effects than fluoxetine or sertraline although specificity for the serotonin receptor limits adverse reactions to serotonergic effects.[7,113,29]

Desvenlafaxine, duloxetine and venlafaxine are SNRIs which are more active at serotonin than norepinephrine receptors. levomilnacipran is more active at norepinephrine receptors. Venlafaxine exhibits serotonergic activity at doses of 75 mg. Doses of at least 225 mg are

associated with inhibition of both SERT and NET activity.[114] Racemic milnacipran is available as the more potent (S)-enantiomer, levomilnacipran which is more active on NET at low doses and both NET and SERT at higher doses.[115] Many of the SNRIs are structurally dissimilar but are believed to act via a common mechanism. Pseudo-anticholinergic side effects are more common with SNRIs than SSRIs secondary to the stimulation of sympathetic noradrenergic receptors producing a relative decrease in parasympathetic tone.[116]

The dual-acting agents have different affinities and selectivities for the norepinephrine and serotonin receptors. Norepinephrine:Serotonin receptor affinity ratios are highest with venlafaxine (15:7), desvenlafaxine (13:8), duloxetine (9:3) and milnacipran 2:1. Receptor selectivity (serotonin:norepinephrine) for venlafaxine is 30, duloxetine is 10, milnacipran is 1 and desvenlafaxine binds norepinephrine 3-fold higher than serotonin. Venlafaxine demonstrates activity at norepinephrine receptors only with higher doses.[112]

Pharmacokinetics

The selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors are highly bioavailable, well absorbed, have large volumes of distribution and undergo hepatic metabolism. Protein binding is higher for selective serotonin reuptake inhibitors than serotonin/norepinephrine reuptake inhibitors, except duloxetine. Peak plasma concentrations are reached in 2-10 hours. The half-life of the selective serotonin reuptake inhibitors ranges from 15-30 hours and the serotonin/norepinephrine reuptake inhibitors from 6-12 hours. The exception is fluoxetine with a half-life of the parent compound of 4-6 days and of the active metabolite (norfluoxetine) of 9 days. See Table 11 for a comparison of the pharmacokinetics of the agents. Drug interactions may occur secondary to the effects of these agents on the metabolism other medications dependent upon the cytochrome P450 isoenzyme system. CYP2D6 inhibition by SSRIs results in reduced metabolism and increased plasma levels of a number of cardiovascular agents (e.g. beta blockers, type IC antiarrhythmic, verapamil).[112,117,118]See Table 12 for a summary of these effects.[6,29] Additionally, a significant drug-food interaction occurs with grapefruit juice resulting in increased absorption of citalopram, escitalopram, fluvoxamine, levomilnacipran, sertraline and venlafaxine which may affect efficacy and toxicity[8,119,120]

Table 11: Pharmacokinetics

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
Serotonin Reuptake Inhibitors					
Citalopram	BA: 80% Tmax: 4 hr	Vd: 12 L/kg PB: 80%	N-demethylation (CYP3A4 and CYP2C19 isoenzymes), deamination, N-oxidation Active: Demethylcitalopram didemethylcitalopram	Fecal Renal < 20%	35 hr
Escitalopram	BA: IV-80% Tmax: 5 hr	Vd: 12 L/kg PB: 56%	P450 CYP3A4 and CYP2C19; N-demethylation Minimally active metabolites	Renal: 10%	27-32 hr
Fluoxetine	BA: 100% Tmax: 6-8 hr	Vd: 1000-7200 L PB: 95%	Extensive: P450 CYP2D6, demethylation Active: Norfluoxetine	Renal	4-6 days Metabolite: 9.3 day
Fluvoxamine	BA: IR: 53% ER: 84% Tmax: 3-8 hr IR: 3-8 hr	Vd: 25 L/kg PB: 80%	Extensive: oxidative demethylation and deamination Active: Fluvoxamine acid (weak)	Renal: 94%	IR: 15.6 hr ER: 16.3 hr
Paroxetine Hydrochloride **Paroxetine Mesylate**	BA: 100% Tmax, controlled-release: 6-10 hr Tmax, regular release: 5.2 to 6.4 hours Paroxetine mesylate: 6-8.1 hr	Vd: Extensive PB: 95%	Extensive: CYP2D6, oxidation and methylation	Fecal: 36% Renal: 64%	Paxil: 21 hr Paxil CR: 15 to 20 hr Pexeva: 33.2 hr Brisdelle: 33.2 hr
Sertraline	BA: 100% Tmax: 4.5-8.4 hr	Vd: 20 L/kg PB: 98%	Glucuronide conjugation, hydroxylation, N-demethylation, oxidative deamination, and reduction Active: N-desmethylsertraline	Fecal: 40-50% Renal 40-45%	26 hr
Serotonin/Norepinephrine Reuptake Inhibitors					

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
Desvenlafaxine (Khedezla®, Pristiq®) **Desvenlafaxine succinate (Pristiq®)**	BA: 80% Tmax: N/A	Vd: 3.4 L/kg PB: 30%	CYP3A4 Minor CYP2C19 and CYP2D6 Desvenlafaxine succinate: Conjugation primary; CYP2A4 minor	Renal: 45%	10-11 hr
Duloxetine (Cymbalta®, Irenka®)	BA: 30-80% Tmax: 6-10 hr	Vd: 1640 L PB: > 90%	CYP1A2 and CYP2D6 oxidation and conjugation	Renal: 70%	12 hr
Levomilnacipran	BA: 92% Tmax: 6-8 hr	Vd: 387-473 L PB: 22%	Desethylation, mainly by CYP3A4, and hydroxylation with further conjugation	Renal 58%	12 hr
Milnacipran	BA: 85-90% Tmax:2-4 hr	Vd: IV: 400 L PB: 13%	Glucuronidation	Renal 50-60%	6-8 hr
Venlafaxine	F (absolute BA) Regular Release: 12.6% Extended Release: 45% Tmax Immediate release: 2.0 hr Extended release: 5.5 hr	Vd: 7.5 L/kg PB: 27-30%	CYP2D6 Active: O-desmethylvenlafaxine (ODV)	Fecal: 2% Renal 87%	5 hr Metabolite: 11 hr
Combination Products					
Fluoxetine (F) & Olanzapine (O)	BA: Both well absorbed Tmax F: 6h O: 4 hr	Vd: F: 1000 – 7200 L O: 1000 L PB: F: 94.5% O: 93%			

Key: BA=bioavailability, Tmax=Time to maximum concentration; F=absolute bioavailability, Vd=volume of distribution, PB=protein binding, IR=immediate Release, CR=controlled release; ER=extended release; N/A=not available

Table 12: Drug Interaction Potential of SSRI and SNRI Medications from Hepatic Isoenzyme Activity [10-15,17,18,20-24,29,65,106,121-125]

	CYP1A2	CYP2D6	CYP2C9	CYP2C19	CYP3A4
SNRI					
Citalopram	--	Mild	--	--	--
Escitalopram	--	Moderate	--	--	--
Fluoxetine	--	Substantial	Substantial	Moderate	Mild
Fluvoxamine	Substantial	Mild	Substantial	Substantial	Moderate
Paroxetine	--	Substantial	--	--	--
Sertraline	--	Mild	--	--	--
SSRI					
Desvenlafaxine	--	Mild	--	--	--
Duloxetine	Mild	Moderate	--	--	--
Levomilnacipran	--	--	--	--	--
Milnacipran	--	--	--	--	--
Venlafaxine	--	Mild	--	--	--

Drug Interactions

Alosetron: Concomitant use with fluvoxamine is contraindicated due to increased drug exposure and side effects.

Anticoagulant/anti-inflammatory/antiplatelet medications: The concomitant use of selective serotonin reuptake inhibitors or serotonin/norepinephrine reuptake inhibitors with anticoagulants, anti-inflammatory or anti-platelet medications (including aspirin) may increase the risk of bleeding by interference with serotonin reuptake in the platelet, impairing platelet hemostatic activity. An increase in bleeding was noted when an SSRI was used with warfarin (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.01, 6.4 p=0.04).

Carbamazepine: Fluoxetine increases carbamazepine levels by an unknown mechanism.

Clozapine: Levels may be increased when used in combination with citalopram, fluoxetine, fluvoxamine or sertraline which impair clozapine hepatic metabolism.

Cyproheptadine: As a serotonin antagonist it should not be used with SSRI/SNRI antidepressants.

Digoxin: Paroxetine inhibits renal tubular P-glycoprotein excretion of digoxin. Monitor for signs and symptoms of digoxin toxicity and adjust digoxin dosage when indicated.

Disulfiram: Sertraline oral concentrate contains alcohol and concomitant use is contraindicated.

Highly protein bound drugs: Non-significant

Hydantoins (ethotoin, fosphenytoin, phenytoin): Fluoxetine increases hydantoin levels by an unknown mechanism.

Methadone: Metabolism is inhibited by fluvoxamine and may produce toxic methadone levels. Caution is recommended in initiating and discontinuing fluvoxamine therapy in patients receiving maintenance methadone therapy.

Pimozide: Citalopram and sertraline use is contraindicated due to the risk of life-threatening arrhythmias, including torsade de pointes.

QTc prolonging medications:[8-12,14,17,23] QTc prolongation, may occur with citalopram, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine. Of all medications which prolong the QTc interval, citalopram, escitalopram and fluoxetine are among the most potent. These agents should not be used in combination with other QTc prolonging medications (clarithromycin, erythromycin, gatifloxacin, pentamidine, sparfloxacin, chlorpromazine, haloperidol, olanzapine, risperidone, amitriptyline, desipramine, imipramine, sertraline, venlafaxine, droperidol) to avoid the potential for life-threatening ventricular arrhythmias, torsade de pointes or sudden death. Citalopram doses above 20 mg daily are not recommended

The FDA reduced the recommended maximum citalopram dosage from 40 mg to 20 mg daily in order to reduce the risk of QTc prolongation.[8] A recent study evaluated the effects of the FDA-initiated citalopram maximal-dosage limitation. A total of 35,848 VA patients (mean age, 58 years [SD=11]; 92% male) receiving a mean citalopram dose of 64 mg/day (SD=8.3) were followed for 180 days after a safety communication was issued. Prescriptions were reduced to $\leq$ 40 mg/day in 60% of patients. All cause hospitalizations or deaths were higher in the dose-reduction group (adjusted hazards ratio, AHR 4.5, 95% CI 4.1 to 5.0) as well as hospitalizations for depression or death (AHR 2.2, 95% CI 1.8-2.6). Neither mortality or the endpoint of hospitalizations for arrhythmia or all cause death were changed significantly.[126]

Citalopram should not be used in patients with long QT syndrome. Citalopram should be used cautiously in patients receiving other QT prolonging medications, especially in the presence of risk factors for QTc prolongation, including older age, decreased left ventricular ejection fraction, ischemia, bradycardia, hypokalemia, and hypomagnesemia. Electrolyte abnormalities should be corrected before initiating citalopram therapy and monitored during therapy.

Ramelteon: Concomitant use with fluvoxamine is contraindicated due to increased drug exposure and side effects.

Serotoninergic medications: Serotonin syndrome, characterized by the triad of mental status changes, neuromuscular rigidity and autonomic instability potentially resulting in death is thought to result from hyperstimulation of the brainstem $5HT_{1A}$ receptors. The concomitant use of multiple serotonergic agonists may result in the development of serotonin syndrome.[29] Highly serotonergic agents (linezolid, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitripan, sibutramine, amphetamine, dextroamphetamine, benzphetamine, diethypropion, methamphetamine, phendimetrazine, phentermine, and tramadol) should not be taken with SSRI/SNRI antidepressants. Following discontinuation of an MAOI, initiation of an SSRI or SNRI should be delayed at least 14 days. Conversely, due to the long half-life of fluoxetine, initiation of an MAOI following discontinuation of fluoxetine therapy should be delayed at least 5-weeks.[6,12,127]

Tamoxifen: Efficacy may be reduced when used with paroxetine.

Thioridazine: Avoid concomitant use with fluoxetine, fluvoxamine or paroxetine. Following the discontinuation of fluoxetine therapy, the initiation of thioridazine therapy should be delayed 5-weeks Tizanidine: Concomitant use with fluvoxamine is contraindicated due to increased drug exposure and side effects

Tricyclic antidepressants: Tricyclic levels may increase to toxic levels when used with SSRI. The combination is not recommended except in severe, refractory depression

Warfarin: Concentrations of warfarin have increased up to 100% in combination with fluvoxamine. Less significant effects have been reported with sertraline and paroxetine.[128]

Special Populations (Refer to Table 13 for a comparison of the products)

Pregnancy: The use of SSRI/SNRI medications during pregnancy requires careful consideration. All agents are category C except Brisdelle® which is indicated only for vasomotor symptoms in menopause and carries a category X designation. The risk of untreated depression in the mother must be balanced with the effects of fetal exposure. Neonatal growth changes and shorter gestations are associated with depression in pregnancy. Up to 30% of neonates may experience a dose-response discontinuation syndrome that is generally short-lived and resolves within 2 weeks with maternal exposure to SSRI/SNRIs.[129] Exposed neonates may develop complications, including respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. The discontinuation syndrome may result in prolonged hospitalization when respiratory support and tube feeding are required. It is unknown if this reflects a true discontinuation syndrome, a direct effect of the medications or their overlap.[130-132] A systematic review found first-trimester exposure to an SSRI/SNRI associated with a slight increase in risk of cardiovascular malformations and persistent pulmonary hypertension of the newborn.[129] A case-control study found infants exposed to SSRI antidepressants in-utero, after the 20th week of pregnancy had a 6-fold increase in the risk of neonatal persistent pulmonary hypertension.[133] Data with paroxetine yields the most compelling data concerning cardiac malformations, however the information does not define the clinical significance of the abnormality. Current evidence does not support a specific morphological teratogenic risk with SSRI use. As such, discussions between the patient, obstetrician and psychiatrist are encouraged to consider the risk: benefit for treatment of maternal depression to the fetus.[134,135]

Genomic Differences, Citalopram: The concentration of citalopram is affected by genomic variation in hepatic metabolism. In CYP2C19 poor metabolizers, the Cmax was increased 68% and AUC increased 107%.[120,136]

The presence of a GRIK4 gene variant is associated with a slightly better response to citalopram therapy. The presence of the GRIK4 gene in combination with a variant of HTR2A increases the response to citalopram 23%.[137]

Hepatic and Renal Impairment: This class of medications are hepatically metabolized. Some have active metabolites (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, venlafaxine) and hepatic dosing adjustments are recommended for all but levomilnacipran and milnacipran. Patients with renal impairment may require dosing adjustments with SNRIs and paroxetine.

Pediatrics: All the SSRI and SNRI antidepressants carry a Black Box Warning regarding the risk of suicidality in children and young adults.[10-12,15,18-24,138-140] Clinicians should be aware of behavioral side effects that are more likely in younger children. In one study, peripubertal children with obsessive compulsive disorder exposed to antidepressants were at higher risk of conversion to mania compared with affected adolescents and young adults. For children with anxiety disorders or mild depression, the number needed to harm (NNH) was 13 (95% CI 11–

15).[141,142] In children, side effects may be managed by dose adjustment with the goal of finding a therapeutic window that provides an adequate clinical response with acceptable degrees of behavioral activation. If not achievable, rotation to another SSRI or SNRI is indicated.

Geriatric: Reducing the starting dose, extending the dosing interval and limiting the maximal dose are options for initiating treatment with an SSRI in the elderly (except sertraline). Dosing modifications are not required with SNRI agents.

Table 13: Special Populations [8,119,143,144]

	Renal	Hepatic	Pregnancy	Excretion in Breast Milk	Pediatric	Geriatric
Serotonin Reuptake Inhibitors						
Citalopram (Celexa®)	Mild to moderate impairment: No adjustment Severe impairment: Use with caution	Any impairment: Max: 20mg/day QTc prolongation risk ↑	C*	Yes Consider the risk/benefit of therapy	Not established	Age > 60 years Max: 20 mg/day
Escitalopram (Lexapro®)	Mild to moderate impairment: No adjustment Severe impairment: Use with caution	Any impairment: 10 mg/day	C*	Yes Consider the risk/benefit of therapy	Age < 12 years: Not established	Dose: 10 mg/day
Fluoxetine (Prozac®, Sarafem®, Selfemra®)	No adjustment	Any impairment or cirrhosis: Lower dose or less frequent administration	C*	Yes Not recommended	Established only for major depressive disorder ≥ 8 years and OCD ≥ 7 years	Lower dose or less frequent administration
Fluvoxamine (Luvox CR®)	No adjustment	Initiate with 100 mg and titrate cautiously	C*	Yes Consider the risk/benefit of therapy	Established only for OCD at age ≥ 8 years	Initiate with 100 mg/day and titrate cautiously
Paroxetine Hydrochloride (Paxil®, Pexeva®) **Paroxetine Mesylate (Brisdelle®, Pexeva®)**	< 30 mL/min: Initiate with 10 mg/day Max: 40 mg/day	Severe impairment: Initiate with 10 mg/day Max: 40 mg/day	C* X**	Yes Consider the risk/benefit of therapy	Not established	Initiate with 10 mg/day Max: 40 mg/day
Sertraline (Zoloft®)	No adjustment	Initiate with a lower or less frequent dose	C*	Yes	Established only for OCD in age ≥ 6 years	No adjustment

	Renal	Hepatic	Pregnancy	Excretion in Breast Milk	Pediatric	Geriatric
				Consider the risk/benefit of therapy		
Serotonin/Norepinephrine Reuptake Inhibitors						
Desvenlafaxine **(Khedezla®, Pristiq®)** **Desvenlafaxine succinate (Pristiq®)**	30-50 mL/min: 50 mg/day < 30 mL/min or ESRD: 25 mg/day or 50 mg every other day	Moderate to severe impairment: 50 mg/day Max: 100 mg/day	C*	Yes Consider the risk/benefit of therapy	Not established	No adjustment (consider renal function)
Duloxetine **(Cymbalta®, Irenka®)**	CrCl < 30 mL/min: Avoid use	Chronic liver disease or cirrhosis: Avoid use	C*	Yes Exercise caution	Established only for generalized anxiety disorder and major depressive disorder in age ≥ 7 years	No adjustment
Levomilnacipran (Fetzima®)	30-59 mL/min: Max dose 80 mg/day 15-30 mL/min: Max dose 40 mg/day	No adjustment	C*	Unknown Consider the risk/benefit of therapy	Not established	No adjustment (consider renal function)
Milnacipran **(Savella®)**	Mild impairment: No adjustment Moderate impairment: Exercise caution CrCl 5-29 mL/min: Maintenance dose 25 mg twice daily (may increase to 50 mg twice daily) ESRD: Not recommended	No adjustment (exercise caution)	C*	Unknown Not recommended	Not established	No adjustment (consider renal function)

	Renal	Hepatic	Pregnancy	Excretion in Breast Milk	Pediatric	Geriatric
Venlafaxine (Effexor®)	Renal impairment: Reduce the total daily dose by 25-50% Severe Impairment or dialysis: Reduce the total daily dose by ≥ 50%	Mild to moderate impairment: Reduce the daily dose by 50% Severe impairment or cirrhosis: Dose may be reduced by > 50%	C*	Yes Consider the risk/benefit of therapy	Not established	No adjustment (consider renal & hepatic function)

Key: CrCl=creatinine clearance, ESRD=end-stage renal disease, OCD=obsessive compulsive disorder, *=Consider the risk/benefit as 3rd trimester administration has resulted in adverse fetal outcomes; **= Brisdelle only; ESRD=end-stage renal disease.

Clinical Evidence

Pediatric

Pediatric Therapy of Psychiatric Disorders

A report by the Oregon Drug Effectiveness Review Project compared the effectiveness and harms of second-generation antidepressants in the treatment of major depressive disorder, dysthymia, subsyndromal depression, seasonal affective disorder, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder and premenstrual dysphoric disorder. No head-to-head evidence was found for seasonal affective disorder, dysthymia, pediatric major depressive disorder, subsyndromal depression, dysthymia or premenstrual dysphoric disorder. This well done report found evidence to support only fluoxetine use in children based upon its risk: benefit profile. See Appendix I: Summary of Oregon Drug Class Review: Second Generation Antidepressants.[5]

Depressive Disorders

Pediatric patients aged 12-18 years with major depressive disorder that did not respond to initial selective serotonin reuptake inhibitor therapy were equally likely to respond to a different SSRI or venlafaxine.[145] Monotherapy with a different SSRI or venlafaxine extended release (ER) resulted in similar outcomes (48.2% vs 47.0%, p=0.83), but treatment with an SSRI was associated with fewer adverse events than venlafaxine ER. The most effective therapy was the combination of drug and cognitive behavior therapy (54.8% vs 40.5%, p=0.009). No head-to-head evidence is available for major depressive disorders in pediatric populations.

Hetrick et al, 2012 performed a Cochrane Review evaluating newer antidepressants for depressive disorders in children and adolescents.[146] They identified 19 trials of depressive disorders in children age 6-18 years, involving 3,353 participants without comorbidities or significant risk for suicide. Pharmacologic interventions included selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), norepinephrine dopamine disinhibitors (NDDIs) and tetracyclic antidepressants (TeCAs). Antidepressant treatment was associated with a statistically significant reduction in depression severity scores. The study documented a statistically significant reduction in depressive symptoms associated with antidepressant therapy of 3.51 (on a scale of 17-133). Remission rates with antidepressant therapy versus no treatment improved from 380 to 480 per 1000 patients treated. Treatment of young people with antidepressant therapy carried a significant increase risk of suicide-related outcomes (58%), relative risk 1.58 (95% CI 1.02 to 2.45). However, clinical trial effects may not be clinically significant because the patients in the studies were less ill than depressed youth who often have comorbidities or are at increased risk of suicide. Additionally, the absolute response was small. Therefore, the risk: benefit may not favor treatment.

A 2016 network meta-analysis of 34 randomized, controlled trials involving 5260 participants evaluated the efficacy of antidepressant therapy in children and adolescents with major depressive disorder.[147] The antidepressants included were amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline and venlafaxine. Only fluoxetine was found superior to placebo (standard mean difference in depressive symptom score=0.51, 95% credible interval (CrI) 0.99 to -0.03). Discontinuations due to adverse events were more common with

duloxetine and imipramine than fluoxetine and discontinuations compared with placebo were more common with imipramine, venlafaxine and duloxetine.

Generalized Anxiety Disorders

A Cochrane review of pharmacotherapy for anxiety disorders in children and adolescents identified 22 short-term RCTs, (N=2519) of which 15 evaluated the efficacy of a selective serotonin reuptake inhibitor medication.[99] Fourteen trials found medications produced a more favorable response than placebo (58.1% vs 31.5%; NNT=4). Review of 9 studies demonstrated the superiority of medication over placebo across all anxiety disorders. A post-hoc analysis of 7 pediatric OCD studies (N=765) found medication superior to placebo in reducing overall symptom severity (weighted mean difference -4.45 (95% CI, -5.94 to -2.97). Overall withdrawal rate due to adverse events was 4.9% and higher with medication vs placebo therapy. The authors conclude, data is sufficient to support the use of selective serotonin reuptake inhibitors and venlafaxine but not benzodiazepines in pediatric anxiety disorders.

Obsessive-Compulsive Disorder (OCD)

A meta-analysis of therapy of OCD in pediatric patients evaluated 13 studies of 1177 participants.[148] Random effects modeling of the pooled effect size (ES) estimate found both cognitive behavior therapy and pharmacotherapy (buspirone, citalopram, clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline) statistically improved symptoms. Cognitive behavior therapy (ES 1.45; 95% CI, 0.68 to 2.22, p=0.002) was more effective than antidepressant therapy (ES 0.48; 95% CI; 0.36 to 0.61, p<0.001) Multivariate regression analysis found clomipramine statistically superior to selective serotonin reuptake inhibitors [paroxetine (p=0.003), fluoxetine (p<.03), fluvoxamine (p=0.001), sertraline (p<0.001)] although less well tolerated. No difference in efficacy between selective serotonin reuptake inhibitors was found.

A meta-analysis of 12 published, randomized-controlled medication trials in 1,244 children and adolescents with OCD found a medication effect size (expressed as a pooled standardized mean difference for results of all studies) of 0.46 (95% CI 0.37 to 0.55) demonstrating a statistically significant difference between drug and placebo treatments ($z = 9.87$, $p < 0.001$).[142] Differences in absolute response rates (defined as ≥25% decrease in Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS) scores after treatment) between an SSRI and placebo ranged from 16% (sertraline and fluvoxamine) to 24% (fluoxetine), corresponding to a number needed to treat of 4 to 6. A multivariate regression analysis of the data, controlling for other variables, demonstrated clomipramine, a nonselective serotonin reuptake inhibitor (SRI), significantly superior to each of the selective serotonin reuptake inhibitors (SSRIs), whereas SSRIs were comparably effective. In the absence of head-to-head trials, it is not clear if clomipramine is truly superior to SSRIs or, as is more likely, if the meta-analysis reflects the order in which the trials were done and their methodologic rigor. Superior or not, clomipramine is generally not used as the drug of first choice for children because of its frequent adverse event profile and arrythmogenic risk. A limitation of the evidence is that the medication effects were statistically significant but modest, reflecting an improvement of 6 points out of 40 in CY-BOCS scores. According to Stanford Health, a change of 25% in score (10 out of 40) suggests mild to moderate improvement while clinically meaningful improvement is associated with a change of 35-50% in CY-BOCS scores.[149]

The Pediatric Obsessive Compulsive Treatment Study (POTS) compared sertraline monotherapy with cognitive behavior therapy (CBT) or a combination of sertraline and cognitive behavior therapy in 112 youth with OCD. Response was assessed by continuous measures of outcome at 12 weeks of therapy using Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS) scores. Combined treatment was superior to CBT (p=0.008) or sertraline (p=0.006) while sertraline and CBT did not differ (p=0.80). [150]

Adult

Adult Therapy of Psychiatric Disorders

The Oregon Drug Effectiveness Review Project evaluated the second generation antidepressants by systematic review and meta-analysis in 2011.[5] See Appendix 1 for a more detailed summary of the report. Evidence supports similar efficacy among agents in the treatment of major depressive disorder in adults. Weaker evidence supports no difference among agents for treatment of dysthymia, subsyndromal depression, seasonal affective disorder, major depressive disorder in children and generalized anxiety disorder. In the setting of comorbid conditions (e.g. methadone maintenance, cocaine abuse, HIV, multiple sclerosis, arthritis, diabetes, cancer or substance abuse disorder) the second generation antidepressants were shown no more effective than placebo. Medication-associated harms are similar across agents although drug-specific differences in adverse events were noted (e.g. sertraline results in more diarrhea, venlafaxine more nausea and vomiting). The evidence is limited by mostly short-term trials and high drop-out rates. Most evidence comes from efficacy studies which strictly define the patient population, avoiding comorbid conditions or concomitant medications. The applicability of the information is limited by a relative lack of effectiveness studies. As a result, generalizability to real-world practice is cautioned.

Depressive Disorders

A meta-analysis comparing selective serotonin reuptake inhibitor to serotonin/norepinephrine reuptake inhibitors (SNRI) in the treatment of major depressive disorders used a random-effects model in assessing 93 RCTs involving 17,036 participants. A modest efficacy advantage was noted with the dual-mechanism agents. A clinical response was more likely with an SNRI than SSRI (risk ratio, RR 1.059; response rates 63.6% vs 59.3%, p=0.003). The number needed to treat to gain one additional response was 24.[151]

A systematic review and meta-analysis evaluated whether sertraline was superior to other antidepressants at 8 weeks of therapy, supporting its use as the first-line antidepressant in adults with acute major depression.[152] Fifty-six randomized, controlled trials involving 4,333 participants were included in the analysis. Statistical assessment was performed with a random effects analysis with a very conservative, 99% confidence interval. Sertraline was compared with tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), (citalopram, escitalopram, fluoxetine, fluvoxamine and paroxetine), serotonin/norepinephrine reuptake inhibitors (SNRI) (milnacipran, venlafaxine) and a variety of other second-generation antidepressants. Sertraline was found to be superior to the SSRI class [relative risk (RR) 0.88; 99% CI, 0.78 to 0.99; number needed to treat (NNT) = 17] and individually to fluoxetine [RR = 0.88; 99% CI, 0.74 to 0.98, NNT=12]. An additional finding was that long-term compliance rates were higher when fluoxetine was administered weekly rather than daily (85.9% vs. 79.4%), however more patients discontinued weekly therapy due to a lack of efficacy.[153]

A meta-analysis compared venlafaxine with SSRIs in the treatment of major depressive disorder using a random effects model.[154] Venlafaxine was associated with statistically higher rates of remission (odds ratio (OR), 1.13; 95% CI, 1.0 to 1.28; p=0.05), response rate (OR, 1.17; 95% CI 1.03 to 1.34) and rates of discontinuation due to adverse events (OR, 1.41, 95% CI, 1.10-1.79, p=0.006) compared with SSRIs. Venlafaxine was found on subgroup analysis to produce a better response than fluoxetine only (OR, 1.28; 95%, 1.05-1.55; p=0.01). All-cause discontinuation rates were similar among agents.

A systematic review and meta-analysis of 6 trials including 5676 participants was performed by Ali et al in 2011.[155] The efficacy of escitalopram in the treatment of major depressive disorder was compared with citalopram, duloxetine or a serotonin-norepinephrine reuptake inhibitors (SNRIs). Changes in Montgomery-Asberg Depression Rating Scale scores, response and remission rates favored escitalopram over pooled selective serotonin reuptake inhibitor therapy and citalopram individually. There was no difference between escitalopram and serotonin-norepinephrine reuptake inhibitors for any outcome measure. Withdrawal rates for adverse events were statistically higher for venlafaxine, duloxetine and pooled SNRIs

A meta-analysis by Lam et al in 2006[156] evaluated the effect of baseline severity of major depressive disorder on the response to escitalopram or citalopram. Evidence from 3 trials involving 1321 participants found escitalopram was superior to citalopram in producing a 50% reduction in MADRS (Montgomery-Asberg Depression Rating Scale) scores at 8 weeks for at each level of baseline severity. Escitalopram produced a response superior to placebo independent of baseline severity and a greater level of response than citalopram at increasing levels of severity.

Olie et al, 2010[157] evaluated the effects of milnacipran or venlafaxine dosed to 200 mg daily in 195 participants with severe major depressive disorder. At 24-weeks, no difference was found between treatments on MADRS (Montgomery-Asberg Depression Rating Scale) score, response rate or remission rate. Adverse events were similar between treatments.

Two trials evaluated the same population of patients with chronic or recurrent major depressive disorder, with or without comorbidities, with or without early onset disease.[158,159] A total of 665 participants were randomized to combination therapy with escitalopram + placebo or escitalopram + bupropion SR or venlafaxine + mirtazapine. The first study, evaluating early-onset chronic major depressive disorder, found people with early onset disease had a lower socioeconomic status and higher medical and psychiatric disease burdens. After adjusting for covariates, response rates between the three treatment groups did not differ significantly. The second trial[159] found that the presence or absence or comorbid conditions had no effect on response rates to therapy. Each of the three treatment arms performed well regardless of underlying illness. Both trials found no differences in tolerability or adverse events between any treatments.

Two trials of serotonin reuptake inhibitors were performed in older patients.[160,161] One study in 138 patients over 65 years, found no difference between sertraline and citalopram for any measure of efficacy, remitter status or cognitive function. No differences were found in rate

or type of adverse events. A second study in 888 patients over 59 years with major depressive disorder compared sertraline with fluvoxamine. No difference was found in Hamilton Rating Scale for Depression scores. Discontinuation rates were very low (3 patients receiving sertraline and 1 patient receiving fluvoxamine).

Patients (N=777) with major depressive disorder treated with citalopram who could not tolerate or were not responding to initial citalopram therapy were randomized to either bupropion sustained release (SR), sertraline or venlafaxine at doses titrated to 400 mg, 200 mg and 375 mg, respectively.[162] After 9 weeks of therapy, no difference was found between any treatment. Remission rates were assessed by Hamilton Rating Scale for Depression (HSRD-17) and Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16). Remission rates for bupropion SR, sertraline and venlafaxine XR by QIDS-SR-16 were 25.5%, 26.6% and 25.0% and by HRSD-17 were 21.3%, 17.6% and 24.8%, respectively (χ^2=3.649, 2 df, p=0.16). Response rates also did not differ; bupropion SR 26.1%, sertraline 28.2% and venlafaxine XR 28.2%. No differences were found in time to response or time to remission. Additionally, no differences were found between agents comparing tolerability or adverse effects.

An analysis by Eli Lilly and Company pooled data from 5 randomized, controlled trials in which patients had failed antidepressant therapy during a current major depressive episode and were then treated with either fluoxetine, olanzapine or the combination fluoxetine/olanzapine.[163] The mean change in Montgomery-Asberg Depression Rating Scale (MADRS) scores were statistically superior with fluoxetine/olanzapine compared with fluoxetine or olanzapine (-13.0 vs -8.6 vs -8.2, respectively; p<0.001 for each comparison to fluoxetine/olanzapine). Remission rates with fluoxetine/olanzapine were 25.5%, statistically superior to fluoxetine (17.3%, p=0.006) and olanzapine (14.0%, p<0.001). Adverse events occurring at more than 10% in patients receiving combination therapy were weight gain increased appetite, dry mouth, somnolence, fatigue, headache and peripheral edema. Random glucose measures were similar in the olanzapine/fluoxetine group and olanzapine group but higher than with fluoxetine (p=0.02). Random cholesterol was higher with combination therapy than either fluoxetine or olanzapine (p<0.001 for each). Cholesterol measurement increases from normal to high categories were similar in combination and olanzapine groups and both higher than fluoxetine (p=0.017). Weight change was similar between combination and olanzapine therapy and higher than with fluoxetine (p<0.001) with significantly more patients receiving combination or olanzapine therapy gaining >7% body weight compared with fluoxetine (p<0.001).

Post-Traumatic Stress Disorder

The ability of medications to prevent the development of PTSD was explored in a Cochrane Review of nine short-term trials (N=345 participants), which evaluated the ability of medications to prevent the development of PTSD.[90] Moderate quality evidence supported the use of hydrocortisone but no data supported the benefit of propranolol, escitalopram, temazepam or gabapentin in preventing PTSD onset.

A single case-series study (N=32) assessed the efficacy of paroxetine, sertraline and venlafaxine in the treatment of PTSD.[164] Paroxetine and sertraline yielded improvements in each of the three outcome measures; Symptom Severity, Global Assessment of Functioning, and Beck Depression Inventory scores (p<0.001 each measure, each drug). Venlafaxine demonstrated

significant improvement in Symptom Severity and Global Assessment of Functioning ($p<0.05$ both measures) but not depression scores. Discontinuations due to adverse events occurred in 8 patients receiving venlafaxine and none receiving paroxetine or sertraline.

Treatment of Abnormal Vasomotor Function

A Cochrane Review evaluated the use of non-hormonal therapies (clonidine, SSRI, SNRI, gabapentin, Vitamin E, relaxation therapy, magnetic devices and acupuncture) in menopausal women with abnormal vasomotor function and a history of breast cancer.[80] Pharmacotherapy was assessed in 9 of 16 studies. Pooling data was not possible and the strength of evidence, which found that clonidine, SSRIs, SNRIs and gabapentin produced a mild to moderate reduction in symptomatology, were of low quality. Clonidine was commonly associated with adverse events while the SSRIs and SNRIs were well tolerated. The authors suggest that the low cost and availability of SSRI and SNRI medications makes them attractive treatment options in women for whom hormonal therapy is contraindicated. They suggest avoiding paroxetine due to data linking paroxetine use to tamoxifen breast cancer treatment failures.

Neuropathic Pain

A 2011 systematic review from the Oregon Health and Sciences University Drug Effectiveness Review Project (DERP) assessed pharmacotherapy of neuropathic pain.[165] Low to moderate strength evidence found no difference in response (defined as 50% pain reduction) or adverse event withdrawals with gabapentin, pregabalin, lamotrigine or tricyclic antidepressants. Adjusted indirect comparisons of placebo-controlled trials found duloxetine, pregabalin and gabapentin superior to lacosamide and lamotrigine with no difference in adverse events between the agents. No differences were found between pregabalin, duloxetine and gabapentin. Efficacy and safety were not different when duloxetine was used in older versus younger patients. Combination therapy with duloxetine and pregabalin was more effective than monotherapy but associated with a greater incidence of adverse events than monotherapy.

Fibromyalgia

A Cochrane review evaluated the efficacy of serotonin/norepinephrine reuptake inhibitors in the treatment of fibromyalgia.[166] Systematic review identified 10 studies involving 6038 participants. Five studies compared duloxetine to placebo and five studies compared milnacipran to placebo. Together, duloxetine and milnacipran produced modest reductions in pain compared with placebo ($p<0.001$). A 50% reduction in pain was found in 280 per 1000 treated patients compared with 192 per 1000 placebo patients ($p<0.0001$). Relative improvement in fatigue was small with duloxetine and milnacipran compared with placebo (2.5%; $p<0.001$). Disease related quality-of-life improvements were also small compared with placebo (4.6%; number needed to benefit (NNTB) 12, 95% CI 9 to 17; $p<0.001$). Improvements in patient-perceived global improvement, cognitive disturbances and tender point pain thresholds were significant with medication versus placebo therapy ($p<0.001$, each measure). Sleep problems were not improved with medication versus placebo therapy ($p=0.15$). The dropout rate due to adverse events was higher with duloxetine and milnacipran than placebo (RR 18.3, 95% CI 1.53 to 2.18; number needed to harm (NNTH) 11, 95% CI 9-13; $p<0.001$). The rate of serious adverse events did not differ between medication and placebo groups.

In subgroup analysis comparing duloxetine versus milnacipran, duloxetine was statistically superior in measures of reducing mean pain scores and sleep problems (p=0.04, both). No difference between agents was found for 50% pain reduction, fatigue, quality of life or withdrawal rates due to adverse effects.

A 2011 systematic-review and meta-analysis found immediate-release paroxetine superior to amitriptyline in reducing pain and sleep disturbances associated with fibromyalgia (p<0.001 for both).[34] The agents did not differ for measures of fatigue, tender points, depression or measures of global clinical improvement. Pooled trials of milnacipran and duloxetine found both agents superior to placebo in producing a 50% reduction in pain and improvement in patient global impression of change. Although milnacipran demonstrated early improvements in fatigue compared with placebo, these effects were not durable to 24-28 weeks. Indirect meta-analysis of pain reduction in short-term trials found duloxetine superior to milnacipran at 8-15 weeks but not at 28 weeks. Response rates (30% or 50% from baseline) and measures of function were not different between duloxetine and milnacipran. Duloxetine did demonstrate superiority to milnacipran in improving sleep disturbances. Milnacipran produced significant tachycardia compared with placebo (NNH 20.6; 95% CI, 15.1-29.1). Indirect evidence found no difference between duloxetine and milnacipran in overall withdrawal rates, adverse event rates, withdrawal due to adverse events or the incidence of hyperhidrosis, which was more common with both agents than placebo.

A Cochrane review of duloxetine treatment of painful neuropathy, chronic pain or fibromyalgia identified 18 trials of 6407 patients for review.[167] Eight trials were diabetic neuropathy trials and 6 were studies in fibromyalgia. The remainder included depression with symptoms of pain or central neuropathic pain. In diabetic neuropathy, duloxetine doses of at least 60 mg daily were effective over 12 weeks in producing at least a 50% pain reduction (risk ratio (RR) 1.73, 95% CI 1.44 to 2.08; number needed to benefit (NNTB) 5). Duloxetine doses above 60 mg were no more effective than doses of 60 mg. In fibromyalgia, duloxetine produced at least a 50% pain reduction at 12 weeks (RR 1.57, 95% CI 1.20 to 2.06; NNTB 8) and 28 weeks (RR 1.58, 95% CI 1.10 to 2.27). Adverse events occurred with duloxetine in a dose-dependent manner and were more common, but not statistically different than with placebo. Duloxetine discontinuations due to adverse events occurred in 12.6% of patients.

Anxiety Disorders

A Cochrane review of 5 trials in 290 participants evaluated the effectiveness of medication in treating anxiety disorders and comorbid alcohol use disorders was inconclusive. A small amount of limited and low-quality evidence suggested serotonin reuptake inhibitors demonstrated some efficacy with good tolerability; however, data was insufficient to determine differences in efficacy or safety among agents. Overall, evidence is insufficient to support the use of medication therapy for anxiety in the setting of comorbid alcohol use.[101]

A systematic review and meta-analysis of 8 randomized, controlled trials involving 2238 patients compared the use of antidepressants and placebo in the treatment of generalized anxiety disorder.[97] Antidepressant therapy was associated with a reduction in symptoms and an inability to meet diagnostic criteria for generalized anxiety disorder (number needed to treat, NNT=5.15) Short-term treatment with an antidepressant was superior to treatment with placebo in measures

of Clinical Global Impression scale. A pooled relative risk (RR) for non-treatment response was 0.70 (95% confidence interval (CI) 0.62 to 0.79) with a NNT of 5.5 (95% CI 4.1 to 8.4). The NNT ranged between 4 with imipramine to 6.72 with paroxetine with no differences identified between medications. No differences in dropout rates were found between medications and placebo or between individual medications or between individual medications and placebo.

A Cochrane review of 37 RCTs in 5264 participants evaluated pharmacotherapy of social anxiety disorder. Short-term superiority of any medication over placebo was demonstrated from 26 short-term treatment trials.[98] The relative risk of a non-response was 0.64 (95% CI 0.57 to 0.73). Effectiveness was higher with SSRIs than moclobemide ($p<0.00001$) or brofaromine ($p=0.09$). The weighted mean difference (WMD) between medication and placebo for measure of symptom severity favored medications (WMD = -18, 95% CI -25.17 to -10.83) as did measures of symptom clusters, comorbid depressive symptoms and disability. The effects were greater for the SSRIs than other medications. Four maintenance and 4 long-term trials demonstrated the benefits of long-term pharmacotherapy. A limitation of the study was the large publication bias identified.

Obsessive-Compulsive Disorder (OCD)

No difference was found between fluvoxamine, paroxetine or citalopram in the treatment of 30 adults with OCD.[168] Measures of efficacy included Yale-Brown Obsessive Compulsive Scale, Hamilton Rating Scale for Depression and National Institute of Mental Health Obsessive-Compulsive Scale. No patient dropped out due to adverse events.

A Cochrane review of 17 studies, involving 3097 participants found SSRIs more effective than placebo in reducing symptoms of OCD at 6 to 13 weeks of treatment by Yale-Brown Obsessive Compulsive Scale score measures (weighted mean difference (WMD) -3.21, 95% CI -3.84 to -2.57). [169] At the completion of therapy, pharmacotherapy with fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram or escitalopram was associated with higher clinical response rates than placebo (RR 1.84, 95% CI 1.56 to 2.17) Adverse events were mild (nausea, vomiting, insomnia) and significantly more common with pharmacotherapy. No difference between SSRI agents was found.

Safety

Black Box Warning: All SSRI/SNRI antidepressants carry a black box warning concerning the risk of suicide. In short-term studies of psychiatric indications including major depressive disorder, the risk of suicidal thinking and behavior was increased in children, adolescents and young adults over the first few months. The risk did not extend above 24 years of age. The risk was not increased in adults and a protective effect was found in adults >65 years of age. It is recommended that the clinical benefit of antidepressant medication be weighed against this risk in young patients who should be monitored for clinical worsening or emergence of suicidal thoughts or behaviors. Families and caregivers should closely observe the patient and communicate any concerns with the prescriber.

Barbui et al, 2009[170] performed a systematic review of observational trials of depressed individuals and completed suicide or attempt. Analysis was performed based on whether the

person had a current SSRI exposure. More than 200,000 patients were identified in 8 studies who received an SSRI for treatment of severe depression. Exposure to an SSRI increased the risk of completed or attempted suicide in adolescents (odds ratio [OR] 1.92, 95% confidence interval (CI)1.51-2.44). In adults the risk was decreased (OR 0.57, 95% CI 0.47-0.70) and in older patients the use of an SSRI provided a protective effect (OR 0.46, 95% CI 0.27-0.79). When analyzed only for patients that had competed a suicide the risk of exposure in adolescents was (OR 5.81, 95% CI 1.57-21.51), in adults (OR 0.66, 95% CI 0.52-0.83) and in older people (OR 0.53, 95% CI 0.26-1.06).

A large, retrospective, propensity score-matched cohort study (N=162,625) evaluated the relationship between starting doses of antidepressants and the incidence of self-harm in the first year of therapy.[171] Outcomes were assessed in patients receiving modal or higher than modal doses of citalopram, sertraline or fluoxetine (modal doses: 20 mg/day, 50 mg/day and 20 mg/day, respectively). No relationship was noted in patients aged 25-64 years. Higher than modal dosing was initiated in 13.1% of patients aged 10-24 years. Those receiving higher than modal dosing were significantly more likely to engage in self-harm (Harms Ratio, 2.2; 95% CI, 1.6-3.0). Over the first 90 days of therapy, 7 additional cases of self-harm per 1000 treated patients were noted for patients receiving higher than modal vs modal doses of citalopram, sertraline or fluoxetine (number needed to harm, NNH=136). A meta-analysis found higher doses of antidepressants were not associated with improved response rates but higher adverse event rates.[172]

Patients receiving antidepressants should be assessed for suicidal risk. This evaluation should consider their age. Treatment should follow the manufacturer recommendations for starting doses and time-frame for dose escalation to reduce the risk of self-harm, increase the likelihood of continuing therapy long enough to experience a clinical benefit and minimize adverse reactions. Patients started on antidepressant therapy, especially young people should be monitored for suicidal behaviors or actions.

Adverse events with SSRI and SNRIs are similar in type but vary in frequency. See Table 14 for a list of adverse effects.

Table 14: Adverse Effects ǂ

	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Desvenlafaxine	Duloxetine	Levomilnacipran	Milnacipran	Venlafaxine
Cardio-vascular	QT prolongation, hypotension, orthostatic hypotension, tachycardia, bradycardia		Vasodilation, chest pain, hypertension, palpitations	Chest pain, palpitations, vasodilation, hypertension, edema, hypotension, syncope	Vasodilation, chest pain, palpitations, hypertension, tachycardia	Chest pain, palpitations	Orthostatic hypotension, syncope, tachycardia, hypertension	Flushing, increased blood pressure, palpitations	**Orthostatic hypotension (6% to 12%; dose related)** Increased heart rate, tachycardia, palpitation, hypertension, hypotension, increased blood pressure, angina pectoris, chest pain, SV extra systole, syncope, PVC	Palpitations, increased heart rate, hypertension, flushing, increased blood pressure, tachycardia, peripheral edema	Vasodilation, hypertension, palpitations, chest pain, edema, tachycardia
Central Nervous System	**Drowsiness (18%; dose related), insomnia (15%; dose related)** Fatigue, anxiety, agitation, yawning, amnesia, apathy, confusion, depression, lack of concentration, migraine, paresthesia	**Headache (24%), insomnia (7% to 14%), drowsiness (4% to 13%)** Fatigue, dizziness, anorgasmia, abnormal dreams, lethargy, paresthesia, yawning	**Insomnia (10-33%) Headache (21%) Drowsiness , (5-17%), Anxiety (5-15%), nervousness (8-14%), Yawning (<11%)** ------ Dizziness abnormal dreams, abnormality in thinking agitation, amnesia, chills,	**Headache (22% to 35%), insomnia (21% to 35%), drowsiness (22% to 27%), dizziness (11% to 15%), nervousness (10% to 12%)** Pain, anxiety, anorgasmia, yawning, abnormal dreams, abnormal thinking, paresthesia, agitation, apathy, CNS stimulation,	**Drowsiness (15% to 24%), insomnia (11% to 24%), headache (6% to 18%), dizziness (6% to 14%)** Nervousness, anxiety, fatigue, agitation, paresthesia, abnormal dreams, lack of concentration, yawning, depersonalization, myoclonus,	**Insomnia (12% to 28%), headache (25%), dizziness (6% to 17%), fatigue (10% to 16%), drowsiness (2% to 15%)** Malaise, pain, agitation, nervousness, paresthesia, aggressive behavior, hypertonia, hypoesthesia, yawning, anxiety	**Dizziness (10% to 13%), insomnia (9% to 12%)** Drowsiness, fatigue, anxiety, delayed ejaculation, abnormal dreams, anorgasmia, jitteriness, depersonalization, dystonia, vertigo, yawning, disturbance in attention,	**Headache (13% to 14%), drowsiness (9% to 11%; dose related), fatigue (≤7% to ≤11%; dose related)** Insomnia, dizziness, agitation, anxiety, delayed ejaculation, yawning, abnormal dreams, anorgasmia, chills, hypoesthesia, lethargy,	Aggressive behavior, agitation, extra-pyramidal reaction, migraine, outbursts of anger, panic attack, paresthesia, tension, yawning	**Headache (18%), insomnia (12%)** Dizziness, migraine, chills, depression, drowsiness, falling, fatigue, irritability	**Headache (38%), insomnia (15% to 24%), drowsiness (12% to 20%), dizziness (11% to 20%)** Nervousness, abnormal dreams, anxiety, yawning, agitation, depression, twitching, anorgasmia, paresthesia, abnormality in thinking, amnesia, chills,

	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Desvenlafaxine	Duloxetine	Levomilnacipran	Milnacipran	Venlafaxine
			lability, sleep disorder confusion, emotional	chills, depression, hypertonia, psychoneurosis, twitching, amnesia, manic reaction, myoclonus, psychotic reaction, malaise	amnesia, chills, emotional lability, vertigo, confusion, myasthenia		male sexual disorder	paresthesia, rigors, sleep disorder, vertigo			confusion, depersonalization, hypoesthesia, migraine, trismus, vertigo
Derma-tologic	Diaphoresis (11%; dose related) Skin rashes, pruritus	Diaphoresis	Diaphoresis, skin rash, pruritus	Diaphoresis, ecchymoses, acne vulgaris	**Diaphoresis (5% to 14%)** Skin rash, pruritus	**Diaphoresis (4% to 11%)** Skin rash	**Hyperhidrosis (10% to 11%)** Alopecia, skin photosensitivity, skin rash	Diaphoresis, pruritus	Hyperhidrosis, skin rash, pruritus, urticaria, xeroderma	Hyperhidrosis, skin rash, night sweats	**Diaphoresis (10% to 14%)** Pruritus, ecchymosis
Endocrine & Metabolic	Decreased libido, amenorrhea, weight gain, weight loss	Decreased libido, menstrual disease	**Decreased libido (1-11%)** Weight loss hypermenorrhea increased thirst weight gain	Decreased libido, hypermenorrhea, weight loss, weight gain	**Decreased libido (3% to 15%)** Weight gain	**Decreased libido (1% to 11%)** Weight gain	Decreased libido, increased serum cholesterol, increased prolactin, weight gain, hot flash, increased LDL cholesterol	**Weight loss (children and adolescents: 14%, adults: ≥1%)** Decreased libido, orgasm abnormal, hot flash, weight gain	Hot flash, hypercholesterolemia, increase thirst	**Hot flash (12%)** Decreased libido, hypercholesterolemia, weight change	**Weight loss (children & adolescents 18% to 47%)** Decreased libido, hypercholesterolemia, orgasm abnormal, albuminuria, weight gain, increased serum TG
Gastro-intestinal	**Nausea (21%), xerostomia (20%)** Diarrhea, dyspepsia, anorexia, vomiting, abdominal	**Nausea (15% to 18%), diarrhea (6% to 14%)** Xerostomia, constipation, dyspepsia, decreased	**Nausea (12-29%), Diarrhea (8-18%), Anorexia (4-17%), Xerostomia (4-12%),**	**Nausea (34% to 40%), diarrhea (11% to 18%), xerostomia (10% to 14%), anorexia (6% to 14%)**	**Nausea (19% to 26%), xerostomia (9% to 18%), constipation (5% to 16%), diarrhea (9% to 12%)**	**Nausea (13% to 30%), diarrhea (13% to 24%), xerostomia (6% to 16%), dyspepsia (6% to 13%), anorexia**	**Nausea (22% to 26%), xerostomia (11% to 17%)** Constipation, decreased appetite,	**Nausea (18% to 23%), xerostomia (11% to 14%); abdominal pain (13%)**	**Nausea (17%)** Constipation, vomiting, decreased appetite, abdominal	**Nausea (37%), constipation (16%)** Vomiting, xerostomia, abdominal pain, decreased	**Nausea (21% to 35%), xerostomia (12% to 17%), anorexia (8% to 17%)** Constipation, diarrhea,

	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Desvenlafaxine	Duloxetine	Levomilnacipran	Milnacipran	Venlafaxine
	pain, dysgeusia, flatulence, increased appetite, sialorrhea	appetite, vomiting, abdominal pain, flatulence, toothache	Dyspepsia constipation flatulence vomiting dysgeusia, increased appetite	Dyspepsia, constipation, vomiting, abdominal pain, flatulence, dysgeusia, dysphagia, gingivitis	Decreased appetite, dyspepsia, flatulence, abdominal pain, nausea, vomiting, increased appetite, vomiting, dysgeusia	**(3% to 11%)**	vomiting, bruxism	Constipation, diarrhea, vomiting, decreased appetite, dyspepsia, dysgeusia, flatulence	pain, bruxism, flatulence	appetite, abdominal distension, diarrhea, dysgeusia, dyspepsia, GERD	dyspepsia, abdominal pain, vomiting, flatulence, dysgeusia, increased appetite
Genito-urinary	Ejaculatory disorder, dysmenorrhea, impotence	**Ejaculatory disorder (9% to 14%)** Impotence, URTI	Ejaculatory disorder impotence urinary frequency	**Ejaculatory disorder (8% to 11%)** Urinary frequency, sexual disorder, impotence, UTI, urinary retention	**Ejaculatory disorder (13% to 28%)** Male genital disease, female genital tract disease, impotence, orgasm disturbance, dysmenorrhea urinary frequency, urinary tract infection	**Ejaculatory disorder (7% to 19%)** Urinary incontinence (children), impotence	Proteinuria, erectile dysfunction, urinary retention, ejaculation failure, urinary hesitancy	Erectile dysfunction, ejaculatory disorder, urinary frequency	Erectile dysfunction, urinary hesitancy, ejaculatory disorder, testicular pain, hematuria, pollakiuria, proteinuria	Decreased urine output, dysuria, ejaculation failure, ejaculatory disorder, erectile dysfunction, prostatitis, scrotal pain testicular pain, testicular swelling, urethral pain, urinary hesitancy, urinary retention, cystitis, urinary tract infection	**Abnormal ejaculation (8% to 19%)** Impotence, Urinary disorder
Hemato-logic/ Oncologic						Purpura					
Hepatic				Abnormal hepatic function tests			Abnormal hepatic function tests	Increased serum ALT	Abnormal hepatic function tests		
Infection				Viral infection	Infection						

	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Desvenlafaxine	Duloxetine	Levomilnacipran	Milnacipran	Venlafaxine
Neurologic Skeletal Muscle	Tremor, arthralgia, myalgia	Neck pain, shoulder pain, back pain	**Weakness (9-21%), Tremor (3-13%)** Hyperkinesia	**Weakness (14% to 26%)** Tremor, myalgia, hyperkinesia, hypokinesia	**Weakness (12% to 22%), tremor (4% to 11%)** Myalgia, back pain, myopathy, arthralgia	**Tremor (<1% to 11%)** Hyperkinesia, back pain, myalgia, weakness	Tremor, stiffness, weakness	**Weakness (≤7% to ≤11%; dose related)** Tremor, musculo-skeletal pain		Tremor	**Weakness (8% to 19%)** Tremor, neck pain
Ophthalmic	Accommodation disturbance		Visual disturbance	Amblyopia	Blurred vision, visual disturbance	Visual disturbance	Blurred vision, mydriasis	Blurred vision	Blurred vision, conjunctival hemorrhage, dry eye syndrome	Blurred vision	Visual disturbance, accommodation disturbance, mydriasis
Otic			Otalgia, tinnitus		Tinnitus	Tinnitus	Tinnitus				
Renal	Polyuria			Polyuria							
Respiratory	Rhinitis, URTI, sinusitis, cough	Flu-like symptoms, rhinitis, sinusitis, nasal congestion	**Pharyngitis (10-11%)** flu-like symptoms Sinusitis epistaxis	URTI, pharyngitis, flu-like symptoms, laryngitis, bronchitis, dyspnea, epistaxis, cough, sinusitis	Dyspnea, pharyngitis, sinusitis, rhinitis	Epistaxis, sinusitis, rhinitis		Oropharyngeal pain, cough		Dyspnea	Pharyngitis, dyspnea, increased cough
Miscell-aneous	Fever					Fever	Angioedema			Fever	Accidental injury, fever

ǂ - Adverse reactions occurring at a rate ≥ **10% are bolded** and the percentage listed. Adverse reactions with an incidence below 10% are presented un-bolded and without percentages.
Abbreviations: SV – Supraventricular; PVC – premature ventricular contraction; URTI – upper respiratory tract infection; UTI – urinary tract infection; GERD – gastroesophageal reflux disease; TG - triglyceride

Adverse Events

All selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors except fluvoxamine and milnacipran include warnings and precautions for angle closure glaucoma.[10-18,20-24,27,173] The drugs cause pupillary dilation, which may trigger an angle closure attack in a patient with anatomically narrow angles who have not had an iridectomy.

Neurologic adverse effects of the serotonergic antidepressants include headache, sedation, insomnia, dizziness, weakness or fatigue, tremor, and nervousness.[29,112] Seizures are uncommon but have been reported with all of these agents. Venlafaxine use is associated with the highest incidence of seizures among the selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors.[5,26] Serotonin has varying effects on the dopaminergic system. Use of these agents has produced extrapyramidal symptoms such as dystonic reactions, akathisia, dyskinesia, hypokinesia, parkinsonian symptoms and neuroleptic malignant syndrome.[174]

Serotonergic antidepressant use is associated with abnormal bleeding, hyponatremia, activation of mania/hypomania (use cautiously after screening for bipolar illness), suicide risk, seizures, gastrointestinal complaints, such as nausea, diarrhea, constipation, vomiting, and anorexia, serotonin syndrome and withdrawal reactions.[5,26,29,112] The agents should be used with caution in patients with concomitant systemic illness due to limited clinical experience.[6]

With respect to individual agents, paroxetine may cause akathisia, may reduce efficacy of tamoxifen therapy in women with breast cancer, may increase the risk of congenital malformations (esp. cardiovascular) when used in the first trimester of pregnancy, is associated with bone fracture, may be more anticholinergic than other selective serotonin reuptake inhibitors and is associated with more weight gain and sexual dysfunction.[5,26,174-177] Fluoxetine is associated with anxiety, insomnia, rash, allergic reactions (including anaphylaxis) and extended effects due to long elimination half-life.[119,127] Fluoxetine and sertraline may cause altered appetite and weight loss (especially in depressed underweight or bulimic patients).[178] Sertraline may decrease uric acid although the clinical significance remains unknown.[17] Citalopram, escitalopram and fluoxetine produce dose-dependent QT prolongation which can be significant and may result in ventricular arrhythmias including torsade de pointes.[179,180] Paroxetine is associated with weight gain, sexual dysfunction and appears to be more anticholinergic than either fluoxetine or sertraline.[29] Levomilnacipran is the most noradrenergic of the serotonin/norepinephrine reuptake inhibitors.[29]

Hyponatremia at normal doses of serotonergic antidepressants is believed to occur secondary to the inappropriate secretion of antidiuretic hormone (SIADH).[5,26,181,182] It is noted with both selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). The rank incidence was highest with fluoxetine (75.3%), paroxetine (12.4%), sertraline (11.7%) and fluvoxamine (1.5%).[183] Symptoms may be mild with headache, cognitive and memory impairment, confusion, weakness, unsteadiness or progress to hallucinations, syncope, seizure, coma, respiratory arrest and death. Hyponatremia appears to be reversible upon discontinuation of the SSRI or SNRI medication. Risk is greatest in the elderly, in the presence of volume depletion and those taking a diuretic.[8,119]

Withdrawal symptoms associated with the rapid discontinuation of SSRIs or SNRIs may include lightheadedness, dizziness, restlessness, dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy insomnia, hypomania, tinnitus, gastrointestinal symptoms and seizures. [119,127,144,184] A gradual taper is recommended to minimize a withdrawal reaction or recurrence of the underlying illness. Withdrawal reactions are more common with shorter acting agents. [150,180]

Sexual dysfunction may occur with any SSRI, resulting in diminished libido, impotence, ejaculatory disturbance or difficulty achieving orgasm.[5,26,29] Both males and females report sexual side effects with use of SSRI and SNRI antidepressants, which may result in noncompliance. Management includes lowering the dose, weekend drug holidays, treatment with amantadine 100 mg three times daily (TID), bethanecol 25 mg TID, buspirone 10 mg TID or bupropion 100-150 mg daily.[26,29,177,185]

Adverse effects of SSRIs in children and adolescents include gastrointestinal complaints, sleep disturbances (hypersomnia, insomnia, vivid dreams), somnolence, restlessness, headache, appetite changes and sexual dysfunction. The effects are dose-dependent and most patients develop tolerance to the effects. Behavioral activation and hypomania may occur in patients at risk of bipolar illness.[76,186]

The Oregon Drug Class Review: Second Generation Antidepressants report found similar types of adverse events among this class of medications although the rate of adverse events differed.[5] See Appendix 1 for more detailed information. In comparison to the second-generation antidepressant class, venlafaxine was associated with more nausea and vomiting; duloxetine with greater discontinuation rates due to adverse events, venlafaxine the fewest discontinuations due to adverse events and sertraline was associated with an increased incidence of diarrhea. For specific adverse effects venlafaxine had the lowest odds adjusted risk ratio for sudden cardiac death compared with fluoxetine and citalopram. The SSRI class was associated with an increased risk of ischemic stroke. Paroxetine may be associated with more weight gain than other agents. All SSRIs and SNRIs are associated with increased risk of gastrointestinal bleeding. An increased risk of fracture was found with citalopram, fluoxetine, paroxetine and sertraline. Although documented in the literature, evidence linking SSRIs with hyponatremia is lacking. Sexual dysfunction is common with all SSRI and SNRI agents and is most common with citalopram, escitalopram, paroxetine, sertraline, venlafaxine and less common with duloxetine. Paroxetine produces a higher rate of male ejaculatory dysfunction and is associated with breast cancer treatment failures in women receiving tamoxifen. Evidence is insufficient to identify a difference in risk of suicidality among agents. In pediatrics, only fluoxetine demonstrates a positive risk:benefit profile.

Summary:

The selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were developed to target serotonin receptors (as well as norepinephrine for the SNRIs) and improve upon the safety of the tricyclic antidepressants (TCAs). Efficacy rates for the treatment of depression were similar to the TCAs with lower rates of adverse events and toxicity. Each of the SSRI agents, citalopram, escitalopram, fluoxetine,

fluvoxamine, paroxetine, sertraline and the SNRIs, desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine are available in oral formulations, including tablet, capsule, solution, suspension, syrup. Extended/delayed release formulations of fluoxetine, fluvoxamine, paroxetine, desvenlafaxine, duloxetine, levomilnacipran and venlafaxine are available allowing for once daily dosing of all agents except milnacipran (twice daily dosing). Fluoxetine is additionally available as a once-weekly, delayed-release capsule and in combination with olanzapine.

All the agents except milnacipran and fluvoxamine are indicated for treatment of major depressive disorders. Duloxetine is the only agent labeled for the treatment of chronic musculoskeletal pain and diabetic peripheral neuropathy pain. Fluoxetine/olanzapine is the only agent labeled for treatment-resistant major depressive disorder and depressed bipolar I disorder, fluoxetine is the only agent labeled to treat bulimia nervosa and paroxetine mesylate (Brisdelle) is the only agent labeled for the treatment of abnormal vasomotor function in menopause. Other indications covered by this class of agents include anxiety disorders (generalized anxiety disorder, panic disorder, and social phobia disorder) obsessive-compulsive disorder, post-traumatic stress disorder and premenstrual dysphoric disorder.

Clinical guidelines for the pharmacotherapy of depression recommend use of a second-generation antidepressant for the treatment of depression. Adjunctive treatment with another antidepressant or atypical antipsychotic agent, is recommended in patients who are resistant to treatment. Guidelines for the treatment of obsessive-compulsive disorder consider Cognitive Behavior Therapy (CBT) or Exposure and Response Prevention therapy (ERP) first-line treatment modalities with serotonin reuptake inhibitors (SSRIs and SNRIs) recommended first-line for pharmacotherapy. Clomipramine may be more effective than serotonergic agents but adverse events are more significant, relegating it to second-line or augmentation use. Combination therapy with psychological counseling and medication therapy has been found most effective. Guidelines for the treatment of fibromyalgia suggest directing therapy toward the most troublesome symptoms. Amitriptyline, serotonin reuptake inhibitors (duloxetine, fluoxetine, milnacipran most commonly), pregabalin and traditional pain management strategies are recommended. Guidelines for treatment of depressive, bipolar I disorder suggest mood stabilizers may be adequate for depressive episodes and minimize the need for antidepressant therapy. Antipsychotic agents may be used alone or in combination with other mood stabilizers or antidepressants (e.g fluoxetine/olanzapine) to maintain mood stability, control agitation or treat bipolar disorder in patients experiencing loss of efficacy with lithium therapy. Guidelines for the treatment of menopause recommend hormonal therapy as first line. In women unable or unwilling to take hormonal therapy, SSRI, SNRI, clonidine, gabapentin or pregabalin may be alternatives. Paroxetine and fluoxetine should not be used in women with a history of breast cancer receiving tamoxifen. Guidelines suggest for treatment of premenstrual dysphoric disorder, first-line pharmacotherapy includes SSRIs, venlafaxine and clomipramine. PTSD guidelines suggest first-line pharmacotherapy with SSRIs or SNRIs after or with a trial of trauma-focused psychological therapy. Guidelines recommend treatment of anxiety disorders with psychological interventions. First-line pharmacotherapy includes SSRIs, followed by SNRIs, pregabalin or monoamine oxidase inhibitors.

Clinical experience with the second-generation antidepressants has not identified a significant difference among agents for indications in which they are labeled. The majority of comparative evidence evaluated in this report comes from the Oregon Report, systematic reviews and meta-analyses. In pediatrics, only fluoxetine demonstrates a favorable risk:benefit profile. In adults, improvements in depression scores, response rates and remission rates did not differ between SSRIs and SNRIs and where evidence is available, no differences exist among agents.

The SSRI and SNRI agents were found to produce similar types of adverse reactions although the rates varied among individual agents. Venlafaxine has the highest rate of nausea and vomiting, paroxetine more sexual dysfunction, sertraline higher rate of diarrhea, fluvoxamine has the highest mean adverse event incidence rate and venlafaxine results in more discontinuations of treatment due to adverse events. The SSRIs are associated with an increased risk of ischemic stroke. Risk of non-vertebral fractures is increased with SSRI use, which appears to be dose-dependent for citalopram, fluoxetine, paroxetine and sertraline. Gastrointestinal bleeding is increased with use of SSRI/SNRI and increased with concomitant non-steroidal anti-inflammatory (NSAID) use. Sexual dysfunction is common with this class of antidepressants and most common with paroxetine and sertraline. Suicidality is increased in children and young adults but not adults. The risk of suicidal behaviors or thoughts is similar among agents. Increases in weight are more common with paroxetine than fluoxetine or sertraline.

Overall, the second-generation antidepressant SSRI and SNRI agents are effective treatment options for mental health disorders. When compared in clinical trials, the agents demonstrate similar rates of efficacy with varying rates of adverse effects. The second-generation antidepressant products are available in many dosage forms, offer once-daily dosing (except milnacipran) and are recommended in expert guidelines as first-line pharmacotherapy for many indications. Treatment of pediatric, adolescent and young adults must be undertaken with caution due to the risk of suicidal thoughts and behaviors. Treatment must be individualized for each patient, considering treatment history, disease severity, comorbid conditions, age, adverse effect profile, potential drug-drug interactions, patient preference, cost and accompanied by patient education and close monitoring during the initial month of therapy.

Appendix 1: Summary of Oregon 2nd Generation Antidepressant Drug Effectiveness Review Project

Question 1: Do the agents differ in efficacy or effectiveness?

Depressive Disorders

Overall: No significant differences were found among SSRI and SNRI agents in 75 head-to-head trials. Most studies included initial use of antidepressants in patients without comorbidities or other psychiatric disorders. Discontinuation, response and remission rates assessed on multiple diagnostic scales did not differ substantially. Anxiety was often assessed as a secondary measure and no differences were found among agents. Improvements in health-related quality of life measures did not differ between agents. In the subset of recurrent depression, no difference was found in the effectiveness of citalopram or sertraline. Overall, the majority of trials demonstrated similar intermediate outcome measure results without significant differences among agents. The only differences found were for agents not included in this review. Mirtazapine was associated with a more rapid onset of action than fluoxetine, paroxetine or sertraline. Bupropion had less effect on sexual function than escitalopram, fluoxetine, paroxetine and sertraline. Nefazodone resulted in improved sleep quality.

Dysthymia: Inadequate evidence, no head-to-head trials

Subsyndromal Depressive Disorder in Adults: No randomized, head-to-head trials. A non-randomized trial comparing sertraline and citalopram in older patients found no difference between agents in improving depressive symptoms, achieving remission or improving psychosocial functioning.

Major Depressive Disorder in Children and Adolescents: No head-to-head trials. Efficacy information from 3 systematic reviews suggests no difference between citalopram, paroxetine, sertraline, venlafaxine and placebo in improving health outcomes and fluoxetine more efficacious than placebo.

Anxiety Disorders

Generalized Anxiety Disorder: Data was limited to make "firm" comparative efficacy assessments. The efficacy is similar between comparisons of duloxetine and venlafaxine as well as sertraline and paroxetine. A single study found HAM-A reduction greater with escitalopram than paroxetine.

Obsessive-Compulsive Disorder: Data from 3 head-to-head trials failed to find a difference in efficacy between fluoxetine and sertraline, venlafaxine and paroxetine, or escitalopram and paroxetine. A faster response to therapy was found with sertraline over fluoxetine, venlafaxine XR than paroxetine and similar response onsets for escitalopram and paroxetine. Health outcomes were not different between venlafaxine XR or paroxetine.

Panic Disorder: Efficacy was not different between escitalopram and citalopram or paroxetine and sertraline in reducing panic attacks and improving quality of life measures

Post-Traumatic Stress Disorder: Efficacy was not found different in studies comparing citalopram and sertraline, sertraline and nefazodone or sertraline and venlafaxine ER.

Social Anxiety Disorder: Head-to-head trials found comparable efficacy in separate studies comparing paroxetine with either escitalopram or venlafaxine ER. No differences were noted between venlafaxine ER, escitalopram, fluvoxamine, paroxetine or sertraline by network meta-analysis. Meta-analysis comparison of placebo-controlled trials found not differences in efficacy between fluvoxamine, paroxetine and sertraline. Evidence does not support the efficacy of fluoxetine.

Premenstrual Dysphoric Disorder: No head-to head trials. No difference was found between continuous and intermittent dosing strategies in a meta-analysis subgroup assessment.

Question 2. Do the agents differ in safety or adverse event?

Tolerability and Discontinuation Rates: Adverse effects among the 2ng generation agents were similar, most commonly nausea, headache, diarrhea, fatigue, dizziness, sweating, sexual side effects, tremor, dry mouth and weight gain. Each agent was associated with a specific adverse effect spectrum.

Venlafaxine: The rate of nausea and vomiting was higher than other SSRIs (range 8-48%), reaching statistical significance in 6 of 12 studies. Meta-analysis found the relative risk of nausea or vomiting was 1.53 (95% CI 1.26 to 1.86) with a number needed to harm (NNH) of 9 (95% CI 6 to 23). A subset analysis for venlafaxine XR continued to find an increase rate of nausea and vomiting, however statistical difference was not found.

Duloxetine: The overall discontinuation rate (RR 1.57; 95% CI 1.27-1.93) or discontinuation rate due to adverse events (1.16; 95% CI 1.04 to 1.30) were higher with duloxetine than other SSRIs.

Sertraline: An increased incidence of diarrhea, 8% (95% CI 3-11%) with a NNH of 13 was found in comparison that other 2nd generation antidepressants. A study comparing sertraline with fluoxetine, fluvoxamine and paroxetine found diarrhea more frequent in the sertraline-treated patients and abdominal pain more common with the other agents (both $p<0.05$).

Additional Findings:

- Pooled study data from a British Prescription-Event-Monitoring program evaluating use in over 10,0000 patients each for fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine and nefazodone found the most common reasons for drug discontinuation to be nausea and vomiting. The overall mean incidence density per 1000 patient months was highest for fluvoxamine (fluvoxamine 17.6; fluoxetine 7.0; paroxetine 7.6; sertraline 6.2). The most commonly associated adverse events were, nausea and vomiting with venlafaxine; male sexual dysfunction, paroxetine and venlafaxine, sweating, drowsiness, sedation, impotence and ejaculatory failure with paroxetine and mania with fluoxetine. The fewest reports of anxiety and agitation with sertraline and fluoxetine. Death and suicide rates did not differ among drugs. The rate of drowsiness

and sedation with fluvoxamine and paroxetine were significantly higher than with fluoxetine or sertraline.

- Statistically significant differences were noted in trials involving fluvoxamine. Diarrhea was more common with fluvoxamine than citalopram, sweating was more common with paroxetine vs fluvoxamine and nausea was more common with fluoxetine than fluvoxamine treated patients.
- Meta-analysis of 15 fluoxetine vs comparator SSRI RCTs found no differences between agents in discontinuation rates due to adverse events between agents.
- Pooled data analysis of the available studies found statistical differences only for venlafaxine and adverse events (RR 1.42; 95% CI 1.16-1.73) and for lowest discontinuation rates due to lack of efficacy with venlafaxine (RR 0.75; 95% CI 0.53 to 1.05).

Specific Adverse Effects

Sudden Cardiac Risk: A nested, case-control study of > 207,000 patients receiving citalopram, fluoxetine or venlafaxine evaluate the risk of sudden cardiac death or near death. No differences were found between agents. Venlafaxine had the lowest odds adjusted ratio compared with fluoxetine (0.66; 95% CI 0.38 to 1.14) or citalopram (0.89; 95% CI 0.50 to 1.60)

Stroke/Venous Thromboembolic Event (VTE): The use of SSRIs was not associated with an increased risk of a VTE event. Two nested, case control studies found a no relationship between the development of intracerebral or subarachnoid hemorrhage or stroke with SSRIs or antidepressants, respectively. Ischemic stroke was increased in SSRI users' vs remote or nonusers with an adjusted harms ratio of 1.55 (95% CI 1.00-2.39).

Weight Change: Paroxetine was associated with statistically greater weight gain and gain of more than 7% than sertraline or fluoxetine. However, various studies found no statistically or clinically significant differences in weight change among fluoxetine, sertraline, citalopram, paroxetine or fluvoxamine.

Gastrointestinal Bleeding: The use of SSRIs is associated with an increased risk of gastrointestinal bleeding. No difference between agents was identified. In patients not receiving anticoagulants or non-steroidal medications no significant increase was found. Two studies in patients receiving NSAIDs or other drugs found and increase risk of GI bleeding (Adjusted OR 1.43, 95% CI 1.09 to 1.89), in those receiving concomitant NSAIDs (OR 3.17, 95% CI 2.01-5.00) and a protective effect with proton pump inhibitors (OR 0.56, 95% CI 0.24 to 1.30)

Fractures: Evidence suggests SSRIs are associated with a dose-dependent, increased risk of fractures which was highest with citalopram, fluoxetine, paroxetine and sertraline. In two studies, odds ratios ranged from 1.98 to 1.38 or with a 2.35 to 3.36-fold higher incidence of fracture.

Hyponatremia: A large body of evidence documents an association between the use of SSRIs and hyponatremia however, controlled evidence is lacking.

Seizures: Evidence is insufficient. Deliberate, self-poisoning-induced seizures was more common with venlafaxine than TCAs or SSRIS in a recent chart review.

Sexual Dysfunction: All SSRI and SNRI agents are associated with sexual dysfunction. Various trials found higher levels of dysfunction with citalopram, escitalopram, paroxetine, sertraline and venlafaxine while one study found statistically less dysfunction with duloxetine.

Suicidality: Pooled data from more than 40,000 individuals found all drugs associated with increased risk of suicidal/self-harm thoughts or behaviors. For people less than 18 years of age with major depressive disorder, the risk: benefit did not favor the use of citalopram, escitalopram, mirtazapine, paroxetine, sertraline or venlafaxine due to a lack of demonstrated efficacy with these agents. Data was insufficient with fluvoxamine. Only fluoxetine demonstrated a risk: benefit for use. No 2nd generation antidepressant was consistently associated with greater risk. In adults the data is inconsistent. Some studies found risk while others did not. No agent was significantly associated with increased risk either in children or adults.

Summary

Venlafaxine has the highest rate of nausea and vomiting, paroxetine more sexual dysfunction, sertraline higher rate of diarrhea, fluvoxamine has the highest mean adverse event incidence and venlafaxine results in more discontinuations of treatment due to adverse effects. The SSRIs are associated with an increased risk of ischemic stroke. Risk of non-vertebral fractures is increased with SSRI use which appears to be dose-dependent for citalopram, fluoxetine, paroxetine and sertraline. Gastrointestinal bleeding is increased with use of SSRI/SNRI and increased with concomitant NSAID use. Sexual dysfunction is common with this class of antidepressants and most common with paroxetine and sertraline. Suicidality is increased in children and young adults but not adults and is not statistically associated with any specific agent. Weight changes are highest with paroxetine than fluoxetine or sertraline.

Question 3: Are there subgroups of patients in which a particular agent may be more effective or associated with fewer harms?

Elderly: No head-to-head trials comparing efficacy in the young to old. Older women may not respond as well as younger women to MDD or dysthymia treatment with second generation antidepressants. Overall tolerability is similar between young and old. Efficacy evidence supports the use of sertraline and fluoxetine although the efficacy for sertraline is inconsistent.

Young: Only fluoxetine yielded a favorable risk: benefit profile.

Ethnicity: Data is inconclusive, however, Hispanics may not respond as well to therapy as Blacks or Whites.

Sex: No clear differences were noted between gender and efficacy. Differences in adverse events were noted with rates of sexual dysfunction more common in men than women and desvenlafaxine-induced nausea more common in men.

Concomitant Medications: Paroxetine use in women receiving tamoxifen for treatment of breast cancer was associated with increased mortality. The risk was not found for fluoxetine, citalopram, sertraline, fluvoxamine or venlafaxine.

Comorbidities: No studies directly compared agents in settings of specific comorbidities. It appears that efficacy for 2nd generation antidepressants may be lower in patients with a variety of comorbid conditions although evidence is limited and inconclusive.

Appendix 2: Evidence for Major-Depressive Disorder

Reference/ Study Design	Patient Selection	Treatment Intervention	Results	Safety
Cipriani et al, 2016[147] Network Meta-analysis of 34 RCTs N=5260	Children to adolescents with major depressive disorder	Amitriptyline Citalopram Clomipramine Desipramine Duloxetine Escitalopram Fluoxetine Imipramine Mirtazapine Nefazodone Nortriptyline Paroxetine Sertraline venlafaxine	Efficacy (change in depressive symptoms) • Fluoxetine > Placebo (standardized mean difference =0.51, 95% credible interval (CrCI) -0.99 to -0.03)	Tolerability (discontinuations due to adverse events) • Duloxetine > Fluoxetine • Imipramine > Fluoxetine • Imipramine, Venlafaxine, Duloxetine > Placebo
De Silva et al, 2012[154] Meta-analysis 26 trials Randomized, double-blind, head-to-head trials N=5858	Major depressive disorder in adults	Venlafaxine compared with Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Venlafaxine	Achieving Remission • Venlafaxine > Pooled SSRIs ○ OR 1.13 (95% CI 1.0-1.28; p=0.05) Response Rate • Venlafaxine > Pooled SSRIs ○ OR 1.17 (95% CI, 1.03-1.34; p=0.02) • Venlafaxine > Fluoxetine ○ OR 1.28 (95% CI, 1.05-1.55; p=0.01)	All-cause Discontinuation • Venlafaxine = Pooled SSRIs Discontinuation due to AE • Venlafaxine > Pooled SSRIs ○ OR 1.41 (95% CI 1.10-1.79, p=0.06)
Ali et al, 2011[155] Systematic review of pooled and meta-analysis studies 6 studies N=5676	Major depressive disorder	Escitalopram Citalopram Duloxetine SNRI	MADRs score, Response Rate, Remission Rate • Escitalopram > Citalopram (Weighted Mean Difference, WMD) ○ MADRS points: 1.13 to 1.73 ○ Response Rate Difference: 7.0-8.3% • Escitalopram > SSRIs ○ MADRS difference of 1.1 points (p<0.0001) ○ response difference of 5.4% (p<0.0001) ○ remission difference of 3.7% (p<0.006) • Escitalopram = SNRIs	Withdrawal Rates for Adverse Events • Escitalopram < Venlafaxine (p<0.001) • Escitalopram < Duloxetine (p<0.05) • Escitalopram < SSRIs (p<0.0007)

Reference/ Study Design	Patient Selection	Treatment Intervention	Results	Safety
Lam et al, 2006[156] 8 week followup Meta-analysis of 3 trials DB, MC, RCT N=1321	Outpatients with major depressive disorder	Escitalopram 10-20 mg daily Citalopram 20-40 mg daily	Montgomery-Åsberg Depression Rating Scale (MADRS); Pooled data analysis • Difference between citalopram and placebo was constant over time independent of baseline severity • Difference between escitalopram and placebo (p=0.0020) and citalopram (p=0.012) became greater the more severely depressed at baseline. MADRS Total Score reduction of 50% at 8 weeks • Escitalopram > Citalopram at each level of baseline severity	• Not Reported
Olie et al, 2010[157] 24 week followup RCT DB, MC N=195	Adults with moderate to severe major depressive disorder without high suicidal risk	Milnacipran Venlafaxine Each flexibly dosed up to 200 mg daily over 4 weeks	MADRS Score • Milnacipran = Venlafaxine MADRS Response • Milnacipran = Venlafaxine MADRS Remission • Milnacipran = Venlafaxine	Adverse Events • Similar in both groups (nausea, dizziness, headache, hyperhidrosis and genitourinary problems in males only)
Sung et al, 2013[158] 12 and 23 week followup SB, RCT N=665	Adult outpatients with nonpsychotic chronic or recurrent major depressive disorder	Escitalopram + Placebo Escitalopram + Bupropion SR Venlafaxine + Mirtazapine	Combination therapy was not better than monotherapy in patients who had a first episode of MDD before age 18 or those that developed MDD later with respect to response, remission, tolerability of medications, quality of life or retention at 12 or 28 weeks.	No differences in rates of adverse effects or side effect profile of the medications
Morris et al, 2012[159] 16 week acute and 18 week followup SB, RCT N=665	Adult outpatients with chronic and/or recurrent major depressive disorder with or without general medical conditions	Escitalopram + Placebo Escitalopram + Bupropion SR Venlafaxine +Mirtazapine	Combination therapy was not better than monotherapy regardless of the presence of or number of comorbid conditions	No differences in tolerability

Reference/ Study Design	Patient Selection	Treatment Intervention	Results	Safety
Rossini et al, 2005[160] 7 week followup DB, RCT N=888	Age > 59 years with major depressive disorder (DSM-IV)	Sertraline 150 mg daily Fluvoxamine 200 mg daily	Response Rates (HAM-D) • Fluvoxamine 71.8% = Sertraline 55.6% (p=0.12))	Discontinuation due to adverse effects • Sertraline (3 patients) ○ Skin rash (2) ○ Intolerable agitation (1) • Fluvoxamine (1 patient) ○ Nausea (1)
Rocca et al, 2005 [161] 1 year followup DB, RCT N=138	Outpatients , age > 65 years with minor depressive disorder or subsyndromal depressive symptomatology	Citalopram 20 mg daily Sertraline 50 mg daily	Change in Hamilton Rating Score for depression • Citalopram ↓55% = Sertraline ↓ 52.7% Achieve Remitter Status (1 year) • Citalopram (53%) = Sertraline (42%), p=0.3466 Global Assessment of Functioning • Citalopram = Sertraline Changes in Mini-Mental Examination • Citalopram = Sertraline Both significant increase from baseline	Develop at least 1 adverse effect • Citalopram = Sertraline Presence of most common adverse effects (nausea, headache, dizziness, dyspepsia, asthenia, sexual dysfunction) Citalopram = Sertraline
Rush et al, 2006[162] RCT N=727	Major depressive disorder who failed or could not tolerate citalopram	Bupropion SR Sertraline Venlafaxine XR	Remission Rates: ○ No difference [χ^2=3.649, 2 df, p=0.16] QIDS-SR-16 HRSD-17 Bupropion SR 2.13% 25.5% Sertraline 17.6% 26.6% Venlafaxine XR 24.8% 25.0% Response Rates (QIDS-SR-16) ○ No difference Bupropion SR 26.1% Sertraline 26.7% Venlafaxine XR 28.2% Time to response: No difference Time to remission: No difference	Tolerability • No differences Adverse Events • No differences

Reference/ Study Design	Patient Selection	Treatment Intervention	Results	Safety
Trivedi et al, 2009[163] 8 week followup Pooled analysis of 5 Eli Lilly RCTs N=1146	Adults with documented current major depressive disorder treatment failure	Olanzapine Fluoxetine Fluoxetine/Olanzapine	Mean Change in MADRS score • Fluoxetine/Olanzapine -13.0 • Fluoxetine -8.6 (p<0.001 vs F/O) • Olanzapine -8.2 (p<0.001 vs F/O) Remission Rates • Fluoxetine/Olanzapine 25.5% • Fluoxetine 17.3 (p=0.006 vs F/O) Olanzapine 14.0 (p<0.001 vs F/O)	Adverse Events in > 10% patients Fluoxetine/Olanzapine • Weight gain, increased appetite, dry mouth, somnolence, fatigue, headache, peripheral edema Random Glucose, mean change (mg/dL) • Fluoxetine/Olanzapine +7.92 = Olanzapine +9.91 > Fluoxetine +1.62 (p=0.02) Random Cholesterol, mean change (mg/dL) • Fluoxetine/Olanzapine +12.4 • Fluoxetine +2.3, Olanzapine +3.1 (both p<0.001 vs F/O) Treatment Emergent Cholesterol from Normal to High • Fluoxetine/Olanzapine = Olanzapine > Fluoxetine (p=0.017) Mean Weight Change (kg) • Fluoxetine/Olanzapine +4.42 kg • Fluoxetine -0.15 (p<0.001 vs F/O) • Olanzapine +4.63 Patients Gaining ≥ 7% body weight (%) • Fluoxetine/Olanzapine 40.4% • Fluoxetine 2.3% (p<0.001) Olanzapine 42.9%

SB - Single blind; RCT – randomized controlled trial; PC - Placebo controlled, DB – double-blind, HAM-D or HRSD-17 – Hamilton Rating Scale for Depression; GAD – General anxiety disorder; RIMA – reversible monoamine oxidase inhibitors; MAOI – monoamine oxidase inhibitor; SSRI – selective serotonin receptor inhibitor; CGI – Clinical Global Assessment scale; LSAS – Leibowitz Social Anxiety scale; MDD – major depressive disorder; QIDS-SR-16 – Quick Inventory of Depressive Symptomatology, Self-Report; MC - multicenter

Appendix 3: Evidence for Treatment of Post-Traumatic Stress Disorder

Reference/ Study Design	N	Patient Selection	Treatment Intervention	Results	Safety
Smajkic et al, 2009[164] Case series study N=32		Bosnian refugees, surviving ethnic cleansing with PTSD	Sertraline 100 mg Paroxetine 20 mg Venlafaxine 75 mg	Symptom severity, improvement ▪ Sertraline, Paroxetine p<0.001 ▪ Venlafaxine p<0.05 Global assessment of functioning, improvement ▪ Sertraline, Paroxetine P<0.01 ▪ Venlafaxine p<0.05 Beck depression Inventory, improvement ▪ Sertraline, Paroxetine <0.001 ▪ Venlafaxine not significant	Discontinuation due to adverse event ▪ Venlafaxine (8/13) ▪ Paroxetine (0) ▪ Sertraline (0)

Appendix 4: Evidence for Treatment of Obsessive Compulsive Disorder (OCD)

Reference/ Study Design/N	Patient Selection	Treatment Intervention	Results	Safety
Geller et al[142] (2003) N= 1244 Meta-analysis of 12 studies	Children & adolescents With OCD	Fluoxetine Fluvoxamine Paroxetine Sertraline Clomipramine	Effect size (pooled standardized mean difference for all study results) • 0.46 (95% CI, 0.37-0.55) Treatment benefit • Medication > Placebo (z=9.87, p<0.001) Absolute response rate • 16% (sertraline and fluvoxamine) • 24% (fluoxetine) • NNT for SSRI = 4 to 6 • Clomipramine > all SSRI (p=0.002)	No safety data reported

Garcia et al[150] 2010 N=112	Adolescents with OCD	Sertraline CBT + Sertraline CBT Pill placebo	Efficacy: CY-BOCS score at week 12 • Sertraline + CBT > CBT (p=0.003) • Sertraline + CBT > Sertraline (p=0.06) • Sertraline + CBT > Placebo (P<0.01) • CBT = Sertraline (p=0.80) • Sertraline > Placebo (p=0.07) • CBT > Placebo (p=0.03)	No safety data reported
Mundo et al, 1997[168] 10 weeks RCT N=30	Patients with OCD	Fluvoxamine 100-300 mg daily Paroxetine 20-60 mg daily Citalopram 20-60 mg daily	No differences noted between treatment groups for • NIMH-OC • Y-BOCS obsessions • Y-BOCS compulsions • Y-BOCS total scores • HAM-D scores Agents are equivalent	No safety data reported No dropouts due to adverse events
Watson et al[148] 2008 Meta-analysis of 13 RCTs 10 Pharmacologic RCTs N=1016 3 Cognitive Behavioral Therapy RCTs N=161	Pediatric OCD	Buspirone Citalopram Clomipramine Fluoxetine Fluvoxamine Paroxetine Sertraline	OCD Symptom Severity (effect size) • Any treatment, 0.72, p<0.0001 • CBT 1.45, p=0.0002 • Drug effect size ○ Pooled: 0.48, p<0.00001 ○ Clomipramine 0.85, p=0.0018 ○ Fluoxetine 0.51 p=0.0026 ○ Fluvoxamine 0.31, p=0.09 ○ Paroxetine 0.44, p<0.0001 ○ Sertraline 0.47, p=0.0003	No safety data reported

Key: RCT=randomized controlled trial; OCD=obsessive-compulsive disorder; CY-BOCS - Children's Yale Brown Obsessive Compulsive Scale; NIMH-OC - severity of obsessive-compulsive symptoms on the National Institute of Mental Health-Obsessive-Compulsive Scale; Y-BOCS - Yale-Brown Obsessive-Compulsive Scale; HAM-D - Hamilton Rating Scale for Depression clinical efficacy and tolerability.

Appendix 5: Evidence for Treatment of Social Anxiety Disorder

Reference/ Study Design/N	Patient Selection	Treatment Intervention	Results	Safety
Stein et al, 2000[98] Duration varied N=5264 Cochrane Review of 36 RCTs • 17 SSRI • 3 MAOI • 9 RIMA • 9 Other agents	Patients with social anxiety disorders	Therapies included SSRI MAOI (phenylzine) RIMA (moclobemide, brofaromine) Other (benzodiazepines, beta-blocker, buspirone, gabapentin, olanzapine)	Responder status pooled compared to placebo • RR of non-response 0.63 (95% CI, 0.55-0.72) Responder status by treatment (Clinical Global Impressions Scale) • Relative risk of non-response ○ SSRI ▪ RR 0.67 (95% CI, 0.59-0.76) ○ MAOI ▪ RR 0.43 (95% CI 0.24 to 0.76) ○ RIMA ▪ RR 0.74 (95% CI, 0.59-0.91) ○ SSRI > RIMA (p<0.00001) Leibowitz Social Anxiety Scale (LSAS) Response Pooled medication response compared to placebo • Weighted mean difference = -15.56; 95% CI -17.95 to – 13.16). • Effect strongest for SSRI Support for long-term treatment in responders • Data from maintenance studies ○ Risk Ratio: 0.58 (95% CI 0.39 to 0.85) • Data from relapse prevention studies ○ Risk Ratio: 0.33 (95% CI, 0.22 to 0.49)	Not Reported
Schmitt et al, 2004[97] 8-28 weeks	All RCTs using antidepressants in generalized anxiety disorder	Venlafaxine 37.5 mg daily Venlafaxine 75 mg daily	Efficacy (absence of sufficient symptoms to continue to meet diagnostic criteria for GAD)	Dropout Rates

Systematic Review and Meta-analysis 8 RCTs N=2238		Venlafaxine 150 mg daily Venlafaxine 225 mg daily Paroxetine 20 mg daily Sertraline (data not reported) Imipramine 50-100 mg daily Imipramine 143 mg daily Trazodone 225 mg daily Diazepam 26 mg daily Placebo	• Antidepressants: Imipramine, venlafaxine, paroxetine > placebo • NNT 5.15 Pooled relative risk (RR) for non-treatment response • Antidepressants: 0.70 (95% CI, 0.62-0.79) • NNT 5.5 Risk of Non-Response by medication • Venlafaxine ○ RR: 0.68 (95% CI 0.46 to 0.9) ○ NNT 5.00 (95% CI 3.58 to 8.62) • Paroxetine ○ RR: 0.72 (95% CI 0.56 to 0.92) ○ NNT 6.72 (95% CI 3.90 to 24.70) • Imipramine ○ RR: 0.67 (95% CI 0.50 to0.91) ○ NNT 4.0 (95% CI 2.4 to 13.7) Sertraline vs placebo in children and adolescents (N=22) • NNT of 1.22 (95% CI 0.90 to -1.7)	No significant differences between treatments or placebo Imipramine: RR = 0.71 (95% CI 0.41 to 1.24) Venlafaxine: RR = 0.86 (95% CI 0.72 to 1.02) Sertraline: RR = 0.45 (95% CI 0.03 to 5.84) Paroxetine: RR = 1.15 (95% CI 0.74 to 1.78) Paroxetine vs imipramine: RR = 1.62 (95% CI 0.58 to 4.48)

Key: GAD=generalized anxiety disorder; SSRI=selective serotonin reuptake inhibitor; MAOI=monoamine oxidase reuptake inhibitor; RIMA=Reversible Monoamine Oxidase Inhibitor; RCT=randomized, controlled trial; RR=relative risk; LSAS=Leibowitz Social Anxiety Scale; CGI=Clinical Global Impressions scale; NNT=number needed to treat

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