HOW TO USE THIS BOOK

The Clinical Handbook of Psychotropic Drugs uses color coding and icons for intuitive navigation:
- Blue sections contain general information on drugs / treatments and their availability.
- Green sections cover drug action and dosing.
- Red sections outline warnings and precautions.
- Orange sections detail patient-related information, such as considerations for special populations, nursing and patient advice.

This page provides a summary of the colors and icons used.
At the end of each chapter, additional useful sources of information are listed as

Further Reading

General Information / Availability
- Classification, Definition
- Product Availability
- Indications
- General Comments

Pharmacology / Mechanisms of Action
- Pharmacology
- Pharmacological & Psychiatric Effects
- Dosing
- Pharmacokinetics
- Onset and Duration of Action
- Switching, Augmentation Strategies

Patient-Related Issues
- Lab Tests / Monitoring
- Pediatric Considerations
- Geriatric Considerations
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- Nursing Implications, Treatment
- Patient Instructions

Warnings and Precautions
- Adverse Effects
- Contraindications
- Discontinuation Syndrome
- Precautions
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- Drug Interactions
Clinical Handbook of Psychotropic Drugs

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The authors and publisher have made every effort to ensure that drug selections and dosages suggested in this text are in accord with current recommendations and practice at the time of publication.
However, due to changing government regulations, continuing research, and changing information concerning drug therapy and reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage, or for added precautions. The authors and publisher disclaim any responsibility for any consequences which may follow from the use of information presented in this book.

Format: PDF
INTRODUCTION

The Clinical Handbook of Psychotropic Drugs is intended to be a user-friendly and practical resource guide for using psychotropic drugs in any setting. Its content is derived from various forms of published literature (including randomized controlled trials, scientific data such as pharmacokinetic trials, cohort trials, case series, and case reports) as well as from leading clinical experts. We endeavor to continually update this handbook as the psychiatric literature evolves so we can continue to provide evidence-based clinically relevant information that is easily accessed and utilized to aid with patient care decisions. New sections, periodically added, reflect changes in therapy and in current practice.

As in previous editions, charts and tables of comparisons are employed to enable the reader to have quick access to information.

Both American and Canadian trade names are used in the text. Though plasma levels are given in SI units, conversion rates to Imperial US units are available in the text.

Given that changes may occur in a medication’s indications, and differences are seen among countries, specific “indications” listed in this text as “approved” should be viewed in conjunction with product monographs approved in your jurisdiction of interest.

Dose comparisons and plasma levels are based on scientific data. However, it is important to note that some patients will respond to doses outside the reported ranges. Age, sex, and the medical condition of the patient must always be taken into consideration when prescribing any psychotropic agent.

Patient Information Sheets for most drug categories are provided as printable pdf files to facilitate education/counselling of patients receiving these medications. For details, please see p. 373.

For those who like the convenience of electronic resources, the Clinical Handbook of Psychotropic Drugs is also available as an online version that provides even quicker access to all the information in the handbook, with some added extras: (1) An auto-completion powered search function, (2) browse features for generic names, trade names, indications, and interacting agents, (3) column-selector enhancement of comparison charts (dosages, side effects, pharmacokinetics, interactions...) that allows you to choose which information is displayed, and (4) hundreds of additional references. Further details on this can be found at http://www.hogrefe.com/chpd-online/

Over the years, many readers have asked many interesting questions and provided useful comments and suggestions regarding the content and format of the handbook. This input is critical to keeping this handbook current, accurate, and relevant to the readership. We really appreciate the feedback. Please feel free to e-mail me at the address below with your comments and questions for the editors and authors.

Kalyna Z. Bezchlibnyk-Butler
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### ANTIDEPRESSANTS

#### Classification

- Antidepressants can be classified as follows:

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<tr>
<td>Selective Serotonin Reuptake Inhibitors (SSRI)</td>
<td>Citalopram, fluoxetine, paroxetine, escitalopram, fluvoxamine, sertraline</td>
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<td>Norepinephrine Dopamine Reuptake Inhibitor (NDRI)</td>
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<td>Nonselective Cyclic Agents (Mixed Reuptake Inhibitor / Receptor Blockers)</td>
<td>Desipramine, amitriptyline, nortriptyline, imipramine</td>
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<sup>(A)</sup> Cyclic antidepressants are currently classified on the basis of their specificity on the reuptake of brain neurotransmitters. This specificity confers a pharmacologic profile on the drugs that determines their spectrum of activity and adverse effects (see table p. 60).

#### General Comments

- Some antidepressants are associated with restlessness or psychomotor agitation prior to seeing any change in core symptoms of depression. Antidepressants are also associated with a small (2–3%) risk of hostility or suicidal ideation and associated behaviors in children, adolescents, and young adults (aged up to 24 years). Risk for suicide should be closely assessed and monitored during the initial weeks of antidepressant therapy. In patients with major depression and a high risk of suicide, treatment selection should consider safety in overdose (i.e., consider using newer antidepressant agents rather than nonselective cyclic and MAOI antidepressants) and close monitoring.
- Though some randomized double-blind, controlled trials and systematic reviews suggest otherwise, on average, all antidepressants are equally efficacious at reducing symptoms of depression. Overall effects of antidepressants are modest when the effects of publication bias are considered. Compared to placebo, the overall effect size of treatment is reported as being 0.31<sup>[1]</sup>
- A meta-analysis of “new generation” antidepressants found escitalopram and sertraline to have better efficacy or acceptability for treating MDD<sup>[2]</sup>
- Different antidepressant classes may be combined in patients with a partial response or in refractory cases; however, consideration of, and additional monitoring for, the potential interactions such as serotonin syndrome is necessary.
- Prophylaxis of depression is most effective if the therapeutic dose is maintained; continued therapy with all classes of antidepressants has been shown to significantly reduce risk of relapse.
- Tolerance (tachyphylaxis or “poop-out” syndrome) has been reported in 10–20% of patients on various antidepressants, despite adherence to therapy. Possible explanations include adaptations in the CNS, increase in disease severity or pathogenesis, loss of placebo effect, unrecognized rapid-cycling, incorrect diagnosis, comorbid substance use, anxiety disorders, ADHD or eating disorders. [Check compliance with therapy; dosage adjustment may help; switching to an alternate antidepressant (p. 68) or augmentation strategies (p. 70) have also been tried]

#### Therapeutic Effects

- Elevation of mood, improved appetite and sleep patterns, increased physical activity, improved clarity of thinking, better memory; decreased feelings of guilt, worthlessness, helplessness, inadequacy, decrease in delusional preoccupation and ambivalence
**Selective Serotonin Reuptake Inhibitors (SSRI)**

<table>
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<th>Trade Name(B)</th>
<th>Dosage Forms and Strengths</th>
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<tr>
<td>Phthalane derivative</td>
<td>Citalopram</td>
<td>Celexa</td>
<td>Tablets/capsules: 10 mg, 20 mg, 30 mg, 40 mg; Oral disintegrating tablets: 40 mg; Oral solution: 10 mg/5 ml</td>
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<td></td>
<td>Escitalopram</td>
<td>Lexapro(B), Cipralex(C)</td>
<td>Tablets/capsules: 5 mg, 10 mg, 20 mg; Oral solution: 5 mg/5 ml</td>
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<td>Bicyclic</td>
<td>Fluoxetine</td>
<td>Prozac, Sarafem(B)</td>
<td>Capsules: 10 mg, 20 mg, 40 mg; Tablets: 10 mg, 15 mg, 20 mg, 60 mg; Oral solution: 20 mg/5 ml</td>
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<td></td>
<td>Fluoxetine/olanzapine</td>
<td>Prozac Weekly(B)</td>
<td>Delayed-release pellets 90 mg</td>
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<td></td>
<td>Fluvoxamine</td>
<td>Symbyax</td>
<td>Capsules: Fluoxetine 25 mg with 3 mg, 6 mg or 12 mg olanzapine; fluoxetine 50 mg with 6 mg or 12 mg olanzapine</td>
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<td></td>
<td></td>
<td>Luvox</td>
<td>Tablets: 25 mg, 50 mg, 100 mg; Extended-release capsules: 100 mg, 150 mg</td>
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<td>Luvox CR</td>
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<td>Monocyclic</td>
<td>Paroxetine hydrochloride</td>
<td>Paxil</td>
<td>Tablets: 10 mg, 20 mg, 30 mg, 40 mg; Oral suspension: 10 mg/5 ml</td>
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<td>Paroxetine mesylate(B)</td>
<td>Paxil CR</td>
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<td>Sertraline</td>
<td>Pexeva</td>
<td>Tablets: 10 mg, 20 mg, 30 mg, 40 mg</td>
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<td>Zoloft</td>
<td>Capsules/tablets: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg</td>
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<td>Oral solution: 20 mg/ml</td>
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* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. (A) Generic preparations may be available. (B) Not marketed in Canada. (C) Not marketed in the USA. (D) Not approved for depression in the USA.

**Indications**

- Major depressive disorder (MDD)
- MDD, recurrent: Prophylaxis
- Bulimia nervosa (fluoxetine and sertraline)
- Obsessive-compulsive disorder (OCD) (fluvoxamine, fluoxetine, paroxetine, escitalopram, and sertraline)
- Panic disorder with or without agoraphobia (paroxetine, sertraline, fluoxetine)
- Social anxiety disorder (paroxetine, sertraline)
- Posttraumatic stress disorder (PTSD) (paroxetine, sertraline)
- Premenstrual dysphoric disorder (paroxetine, sertraline)
- Generalized anxiety disorder (GAD) (escitalopram, paroxetine)
- Depressive episodes associated with bipolar I disorder and treatment-resistant depression (fluoxetine/olanzapine combination – Symbyax)

* Indications listed here do not necessarily apply to all SSRIs or all countries. Please refer to a country’s regulatory database (e.g., US Food and Drug Administration, Health Canada Drug Product Database) for the most current availability information and indications.
Selective Serotonin Reuptake Inhibitors (SSRI) (cont.)

- Dysthymia
- Depression, atypical
- MDD in patients with comorbid medical disorder (i.e., poststroke depression and crying, myocardial infarction) or psychiatric illness
- Binge-eating disorder: Double-blind studies suggest efficacy of fluvoxamine and citalopram
- Dementia and borderline personality disorder: Treatment of self-injurious behavior, aggression, impulsive behavior, and behavior disturbances
- Smoking cessation and withdrawal from drugs, including alcohol – variable response reported
- Chronic fatigue syndrome: Open label trials have shown 70% effectiveness but randomized controlled trials have not replicated this
- Body dysmorphic disorder – benefit reported
- Postpartum depression – open trial suggests sertraline may prevent recurrence in women with a prior history
- Pervasive developmental disorder (autism) in adults (fluoxetine) and selective mutism – preliminary data suggest efficacy
- Pain management (e.g., diabetic neuropathy, arthritis), phantom limb pain (fluoxetine, sertraline), Raynaud's phenomenon (fluoxetine), fibrositis, and fibromyalgia (fluoxetine) – data conflicting as to efficacy
- Trichotillomania
- Premature ejaculation
- Enuresis, functional – data contradictory as to efficacy; case reports of bedwetting in children treated with SSRIs
- Hot flashes in women in menopause – open label and double-blind studies have found a variable response to SSRIs. About 30% of women showed a 30% reduction in hot flashes, one third had less than 30% reduction and 37% showed an increase in hot flashes. A 2011 randomized, double-blind trial using escitalopram found a favourable statistically significant response over placebo
- Schizophrenia, negative symptoms (fluoxetine)
- Tardive dyskinesia: Case reports suggest fluvoxamine may be helpful due to its potent sigma-1 receptor agonist activity

General Comments

- SSRIs have been associated with increased suicidal ideation, hostility, and psychomotor agitation in clinical trials involving children, adolescents, and young adults (up to 24 years old). This effect was not seen in those aged 24–65 and SSRIs were preventative for these concerns in those over the age of 65. Monitor all patients for worsening of depression and suicidal thinking
- Based on data from observational studies, use of SSRIs may be associated with a reduced risk of suicide in adults with depression. Among adolescents, use of SSRIs may increase suicidality
- In the STAR*D trial, approximately 30% of patients with depression reached remission after 10 weeks of therapy on citalopram (average dose = 42 mg) and 50% had a response

Pharmacology

- Exact mechanism of antidepressant action unknown; SSRIs, through inhibition of serotonin reuptake, increase concentrations of serotonin in the synapse, which causes downregulation of post-synaptic receptors (e.g., 5-HT_{2A}). Some SSRIs can also affect other neurotransmitters, e.g., some SSRIs also inhibit the reuptake of norepinephrine (i.e., fluoxetine, paroxetine), while others inhibit the reuptake of dopamine (i.e., sertraline)

Dosing

- See p. 65
- SSRIs have flat dose-response curves (i.e., most patients respond to the initial or even low doses, such as 5 –10 mg of fluoxetine). Do not increase the dose till steady state is reached (4 weeks for fluoxetine and 1-2 weeks for other drugs)
- Dosage should be decreased (by 50%) in patients with significant hepatic impairment, as plasma levels can increase up to 3-fold
- In kidney impairment, sertraline levels may increase by 50%; use 50% of the standard dose of paroxetine if creatinine clearance is 10–50 ml/min, and 25% of the standard dose if creatinine clearance is < 10 ml/min
- Higher doses may be required in the treatment of OCD, eating disorders, and PTSD
- Lower starting dose may be effective for panic disorder and should be considered, as patients more sensitive to stimulant effects
- Dosing interval of every 2–7 days has been used with fluoxetine in prophylaxis of depression; once weekly dosing used in the maintenance treatment of panic disorder
- Intermittent dosing (during luteal phase of menstrual cycle) found effective for the treatment of premenstrual dysphoric disorder
Pharmacokinetics
- SSRIs are absorbed relatively slowly but completely (time to peak plasma concentration is 3–8 h); undergo little first-pass effect
- Highly bound to plasma protein (fluoxetine, paroxetine, and sertraline) and will displace other drugs from protein binding although this is rarely clinically significant (see Interactions, p. 10)
- Metabolized primarily by the liver; all SSRIs affect CYP450 metabolizing enzyme (least: citalopram and escitalopram) and will affect the metabolism of other drugs metabolized by this system (see Interactions, p. 10). Fluoxetine and paroxetine have been shown to decrease their own metabolism over time. Clearance of all SSRIs reduced in patients with liver cirrhosis
- Peak plasma level of sertraline is 30% higher when drug taken with food, as first-pass metabolism is reduced
- Fluoxetine as well as its active metabolite, norfluoxetine, have the longest half-lives (up to 70 h and 330 h, respectively); this has implications for reaching steady-state drug levels as well as for drug withdrawal and drug interactions
- Controlled-release paroxetine is enteric-coated and formulated for controlled dissolution; it has been suggested to be better tolerated than the regular-release preparations in regards to GI effects, especially at start of therapy
- Once weekly dose of delayed-release fluoxetine 90 mg results in similar mean steady-state plasma concentration of fluoxetine and norfluoxetine, achieved with a daily dose of 10–20 mg; peak to trough differences vary (rates of nausea appear to be similar with immediate-release and controlled-release preparations)

Onset & Duration of Action
- SSRIs are long-acting drugs and can be given in a single daily dose, usually in the morning; fluvoxamine and sertraline may cause sedation and can be prescribed at night
- Therapeutic effect typically seen after 28 days (though some patients may respond sooner); most patients with depression respond to the initial (low) dose; increasing the dose too rapidly due to absence of therapeutic effect or adverse effects can result in higher doses than necessary being used and higher rate of adverse effects
- Tolerance to effects seen in some patients after months of treatment (“poop-out syndrome” or tachyphylaxis) (see p. 2)

Adverse Effects
- The pharmacological and side effect profile of SSRIs is related to their in vivo affinity for and activity on neurotransmitters/receptors (see Table p. 60)
- For incidence of adverse effects at therapeutic doses see chart (p. 63)
- Incidence may be greater in early days of treatment; patients adapt to many side effects over time
- Rule out withdrawal symptoms of previous antidepressant – can be misattributed to side effects of current drug

CNS Effects
- Headache common, worsening of migraines [Management: acetaminophen prn]
- Seizures reported, primarily in patients with underlying seizure disorder (risk 0.04–0.3%)
- Both activation and sedation can occur early in treatment
- Activation, excitement, impulse dyscontrol, anxiety, agitation, and restlessness; more frequent at higher doses [may respond to lorazepam]; psychosis or panic reactions may occur; isolated reports of antidepressants causing motor activation, aggression, depersonalization, suicidal urges, and potential to harm others. CAUTION in children and adolescents (see p. 9)
- Insomnia: Decreased REM sleep, prolonged sleep onset latency, reduced sleep efficacy, and increased awakenings with all SSRIs; increased dreaming, nightmares, sexual dreams and obsessions reported with fluoxetine [may respond to clonazepam or cyproheptadine 2–4 mg]; case reports of somnambulism with paroxetine
- Drowsiness – more common with fluvoxamine and sertraline; prescribe bulk of dose at bedtime; sedation with fluoxetine may be related to high concentration of metabolite norfluoxetine
- Precipitation of hypomania or mania (up to 30% of patients with a history of bipolar disorders – less frequent if patient receiving mood stabilizers); increased risk in patients with comorbid substance abuse
- Lethargy, apathy or amotivational syndrome (asthenia) reported – may be dose related and is reversible; more likely with SSRIs than SNRIs [prescribe bulk of dose at bedtime; amantadine (100–200 mg/day), bupropion, buspironie, modafinil (100–400 mg/day), or psychostimulant (e.g., methylphenidate 5–20 mg bid) or consider alternate agent]
- Case reports of cognitive impairment, decreased attention and short-term memory [early data suggest donepezil 2.5–10 mg/day may be of benefit]
- Case reports of visual hallucinations with fluoxetine, fluvoxamine, paroxetine, and sertraline
- Fine tremor [may respond to dose reduction or to propranolol]
- Akathisia [may respond to dose reduction, to propranolol or to a benzodiazepine]
Selective Serotonin Reuptake Inhibitors (SSRI) (cont.)

- Dystonia, dyskinesia, parkinsonism or tics; more likely in older patients
- Increased extrapyramidal symptoms reported in patients with Parkinson's disease
- Case reports of tardive dyskinesia following chronic fluoxetine, sertraline, and paroxetine use; more likely in older patients
- Tinnitis
- Myoclonus (e.g., periodic leg movements during sleep); may increase spasticity; recurrence of restless legs syndrome
- Dysphasia, stuttering
- May induce or worsen extrapyramidal effects when given with antipsychotics (see Interactions p. 12)
- Impaired balance reported, especially in the elderly
- Nocturnal bruxism reported – may result in morning headache or lead to damage to teeth or bridgework [may respond to buspirone up to 50 mg/day]
- Paresthesias; may be caused by pyridoxine deficiency [Management: Pyridoxine 50–150 mg/day]; “electric-shock-like” sensations
- Joint pain
- Cerebrovascular disease and case reports of stroke (high doses of high-affinity SSRIs can increase risk of bleeding or vasospasm due to antiplatelet effect or serotonergic overstimulation)
- Anticholinergic Effects
  - Case reports of urinary retention, urgency, incontinence or cystitis
  - Case report of acute angle closure with paroxetine in patient with narrow-angle glaucoma
- Cardiovascular Effects
  - Citalopram and escitalopram cause dose-dependent QT interval prolongation. Citalopram should no longer be prescribed at doses greater than 40 mg/day, and 20 mg/day in patients above age 60 (65 in Canada), in individuals with liver impairment, or if combined with CYP2C19 inhibitors. Similarly, the dose of escitalopram should be limited to 20 mg/day in individuals with liver impairment and to 10 mg/day if combined with CYP2C19 inhibitors. Citalopram use is discouraged in patients with congenital long QT syndrome. Patients with congestive heart failure, bradyarrhythmias, or predisposition to hypokalemia or hypomagnesemia because of concomitant illness or drugs are at higher risk of developing torsades de pointes
  - Rare reports of tachycardia, palpitations, hypertension, and atrial fibrillation
  - Bradycardia
  - Dizziness
  - May cause coronary vasoconstriction; caution in patients with angina/ischemic heart disease
  - Slowing of sinus node reported with fluoxetine; caution in sinus node disease and in patients with serious left ventricular impairment; case reports of QT prolongation with fluoxetine (two mechanisms proposed: Direct blockade of the hERG potassium ion channels and disruption of hERG protein expression on the cell membrane)
  - Increased LDL cholesterol levels reported with paroxetine and sertraline
  - In a meta-analysis of SSRIs in patients with depression and coronary heart disease, SSRIs were found to decrease depressive symptoms with no significant difference in mortality or readmission rates
- Hematologic Effects
  - Bleeding disorders including petechiae, purpura (1% risk with fluoxetine); thrombocytopenia with fluoxetine; bruising, nosebleeds, and bleeding after surgery reported with all SSRI drugs; increased bleeding attributed to inhibition of serotonin uptake by platelets; increased GI bleed attributed to increase in gastric acid secretion; risk increased in older individuals, those with a history of GI bleed or in combination with drugs such as NSAIDs, ASA, anticoagulants or antiplatelet drugs (see Interactions p. 10–15); GI bleed risk decreased with use of proton pump inhibitors
  - Rare blood dyscrasias including neutropenia and aplastic anemia
- Endocrine & Metabolic Effects
  - Can induce SIADH with hyponatremia; can result in nausea, fatigue, headache, cognitive impairment, confusion, and seizures; risk increases with age (up to 32% incidence), female sex, low body weight, smoking and concomitant diuretic use
  - Monitoring of serum sodium is suggested in the elderly, those with a history of hyponatremia or on other agents associated with hyponatremia, such as diuretics, or with comorbid conditions associated with hyponatremia, such as heart failure
  - Elevated prolactin – risk increased in females (up to 22% reported in women on fluoxetine); cases of galactorrhea reported; breast enlargement; case of gynecomastia in a male on paroxetine – not related to dose
  - SSRIs don’t typically affect blood glucose; however, case reports of increases have occurred in patients taking paroxetine and other antidepressants associated with weight gain
Other Adverse Effects

- Hypersensitivity Reactions
  - Rash (up to 1% incidence), urticaria, psoriasis, pruritus, edema, photoallergy/photosensitivity (cross-sensitivity between SSRIs has been suggested); rare cases of Stevens-Johnson syndrome
  - Serum sickness, toxic epidermal necrolysis (fluvoxamine)
  - Increased hepatic enzyme levels, bilirubinemia, jaundice, hepatitis

- Urogenital & Sexual Effects
  - A result of inhibition of 5-HT reuptake (activation of 5-HT₂ receptors)
  - Nausea; vomiting – generally decreases over time due to gradual desensitization of 5-HT₃ receptors [may respond to taking drug with meals or switching to the delayed/controlled-release preparation; cyproheptadine 2 mg or lactobacillus acidophilus (e.g., yogurt)]
  - Diarrhea, bloating – usually transient and dose-related; may be more frequent with fluoxetine 90 mg given weekly
  - Anorexia and weight loss frequently reported during early treatment – more pronounced in overweight patients and those with carbohydrate cravings
  - 2–4 times higher risk of upper GI bleeding with SSRIs, especially if combined with NSAIDs (risk increased 12-fold) or ASA
  - Case reports of stomatitis with fluoxetine; glossodynia (burning mouth syndrome) reported during treatment with fluoxetine, sertraline

- GI Effects
  - A result of inhibition of 5-HT reuptake (activation of 5-HT₁ receptors)
  - Nausea; vomiting – generally decreases over time due to gradual desensitization of 5-HT₃ receptors [may respond to taking drug with meals or switching to the delayed/controlled-release preparation; cyproheptadine 2 mg or lactobacillus acidophilus (e.g., yogurt)]
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  - Case reports of stomatitis with fluoxetine; glossodynia (burning mouth syndrome) reported during treatment with fluoxetine, sertraline

- Other Adverse Effects
  - Case reports of alopecia
  - Rhinitis common
  - Case reports of exacerbation of Raynaud’s syndrome
  - Several cases of decreased thyroid indices reported with sertraline
  - Nocturia (in up to 16% of patients)
  - Osteoporosis: Rate of bone loss higher in SSRI users; increased risk of fractures in women and older adults
  - There is a growing body of evidence to suggest an increased, dose-dependent risk of fractures among patients taking SSRIs. When prescribing SSRIs, the increased risk of fractures must be considered, including risk of falls and potential fracture risk
  - Amongst all SSRIs, sweating is most likely with paroxetine (a result of NE-reuptake inhibition) [Management: Daily showering, talcum powder; in severe cases: Drysol solution, oxybutynin up to 5 mg bid, clonidine 0.1 mg bid, guanfacine 2 mg hs, benztrapine 0.5 mg hs; drug may need to be changed

- Hypersensitivity Reactions
  - Rare
  - Rash (up to 1% incidence), urticaria, psoriasis, pruritus, edema, photoallergy/photosensitivity (cross-sensitivity between SSRIs has been suggested); rare cases of Stevens-Johnson syndrome
  - Serum sickness, toxic epidermal necrolysis (fluvoxamine)
  - Increased hepatic enzyme levels, bilirubinemia, jaundice, hepatitis

- Urogenital & Sexual Effects
  - A result of increased serotonergic transmission by way of the 5-HT₂A receptor which results in reduced dopaminergic transmission, acetylcholine (ACh) blockade, and reduced nitric oxide levels – appears to be dose-related; risk increased with age and concomitant drug use
  - All three phases of the sexual cycle may be affected: Reduced interest and desire for sex; erectile dysfunction in men and diminished arousal in women; and difficulty in attaining orgasm in both sexes; reducing the dose is helpful in some (but not all) cases
  - Paroxetine may be more likely than other SSRIs to cause sexual dysfunction and fluvoxamine may have a modest advantage
  - The phosphodiesterase inhibitors such as sildenafil have been shown by double-blind randomized placebo-controlled trials to be effective in overcoming erectile dysfunction and orgasmic dysfunction problems induced by SSRIs in men, and in reducing adverse sexual effects including reversal of anorgasmia in women, with similar adverse events to the general population
  - Decreased libido, impotence, ejaculatory disturbances occur relatively frequently [Management: Sildenafil (25–100 mg prn), amantadine (100–400 mg prn), bethanechol (10 mg tid or 10–50 mg prn), cyproheptadine (4–16 mg prn – sedation and/or loss of antidepressant response reported occasionally), neostigmine (7.5–15 mg prn), yohimbine (5.4–16.2 mg prn or 5.4 mg tid – may cause anxiety/agitation), buspirone (15–60 mg od or prn), bupropion (75–300 mg/day – results contradictory), or “drug holidays” (i.e., skip dose for 24 h prior to sexual activity; not effective with fluoxetine)
  - Anorgasmia or delayed orgasm [Management: Amantadine (100–400 mg prn); cyproheptadine (4–16 mg prn – sedation and/or loss of antidepressant response reported occasionally), bupropion (15–60 mg od or prn), bupropion (75–300 mg od – results contradictory); mirtazapine (15–45 mg od), yohimbine (5.4–10.8 mg od or prn – may cause anxiety/agitation); methylphenidate (5–40 mg od), dextroamphetamine (5–40 mg od), ginseng, sildenafil (25–150 mg prn)]
  - Spontaneous orgasm with yawning
  - Cases of priapism in both males and females reported with citalopram, fluoxetine, and sertraline

- GI Effects
  - A result of inhibition of 5-HT reuptake (activation of 5-HT₃ receptors)
  - Nausea; vomiting – generally decreases over time due to gradual desensitization of 5-HT₃ receptors [may respond to taking drug with meals or switching to the delayed/controlled-release preparation; cyproheptadine 2 mg or lactobacillus acidophilus (e.g., yogurt)]
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  - Amongst all SSRIs, sweating is most likely with paroxetine (a result of NE-reuptake inhibition) [Management: Daily showering, talcum powder; in severe cases: Drysol solution, oxybutynin up to 5 mg bid, clonidine 0.1 mg bid, guanfacine 2 mg hs, benztrapine 0.5 mg hs; drug may need to be changed
Selective Serotonin Reuptake Inhibitors (SSRI) (cont.)

Discontinuation Syndrome

- Abrupt discontinuation of high doses may cause a syndrome consisting of somatic symptoms: Dizziness (exacerbated by movement), lethargy, nausea, vomiting, diarrhea, headache, fever, sweating, chills, malaise, incoordination, insomnia, vivid dreams; neurological symptoms: Myalgia, paresthesias, dyskinesias, "electric-shock-like" sensations, visual discoordination; psychological symptoms: Anxiety, agitation, crying, irritability, confusion, slowed thinking, disorientation; rarely aggression, impulsivity, hypomania, and depersonalization; cases of mania reported following antidepressant taper, despite adequate concomitant mood-stabilizing treatment
- Most likely to occur within 1–7 days after a short half-life drug stopped or dose drastically reduced, and typically disappears within 3 weeks
- Incidence (of 2–78%) is related to half-life of antidepressant – reported most frequently with paroxetine, least with fluoxetine; attributed to rapid decrease in 5-HT availability
- Therefore these medications should be withdrawn gradually after prolonged use. Taper antidepressant no more rapidly than by 25% per week (or nearest dose possible) and monitor for recurrence of depressive symptoms (except for fluoxetine, which can be tapered more rapidly due to its prolonged half-life)

Management

- Re-institute drug and taper more slowly
- Report that ginger can mitigate nausea and disequilibrium effects; substitution with one dose of fluoxetine (10–20 mg) also recommended to help in the withdrawal process

Precautions

- Monitor all patients for worsening depression and suicidal thinking especially at start of therapy or following an increase or decrease in dose; see comments under Pediatric Considerations, p. 9
- May impair the mental and physical ability to perform hazardous tasks (e.g., driving a car or operating machinery)
- May induce manic reactions in up to 20% of patients with bipolar disorder – reported more frequently with fluoxetine; because of risk of increased cycling, bipolar disorder is a relative contraindication unless a mood stabilizer is added
- Use of SSRIs with other serotonergic agents may result in a hypermetabolic serotonin syndrome – usually occurs within 24 hours of medication initiation (but can occur within minutes to hours), overdose or change in dose. Symptoms include: Nausea, diarrhea, chills, sweating, dizziness, elevated temperature, elevated blood pressure, palpitations, increased muscle tone with twitching, tremor, myoclonic jerks, hyperreflexia, unsteady gait, restlessness, agitation, excitation, disorientation, confusion and delirium; may progress to rhabdomyolysis, coma, and death (see Interactions) [Treatment: Stop medication and administer supportive care, cyproheptadine 4–16 mg may reduce duration of symptoms]. Residual symptoms such as muscle aches may last for up to 8 weeks in SSRIs with long half-lives
- Fluoxetine, paroxetine, and sertraline will displace drugs from protein binding and may elevate the plasma levels of the displaced drug(s)
- Fluoxetine, fluvoxamine, and paroxetine affect CYP450 and will inhibit the metabolism (and elevate the levels) of drugs metabolized by this system; sertraline will inhibit metabolism in higher doses (over 100 mg/day) (see Interactions, pp. 10–15)
- Combination of SSRIs with other cyclic antidepressants can lead to increased plasma level of other antidepressants. Combination therapy has been used in the treatment of resistant patients. Caution when switching from fluoxetine to another antidepressant (see Interactions). Caution when switching from one SSRI to another

Toxicity

- SSRIs generally have a low probability of causing dose-related toxicity; symptoms include: Nausea, vomiting, tremor, myoclonus, irritability (one fatality reported with dose of 6000 mg of fluoxetine; seizure reported in adolescent after ingestion of 1880 mg)
- Rapid onset of seizures with QTc interval prolongation is common with citalopram; citalopram and escitalopram are more likely to cause cardiotoxicity than other SSRIs. Cardiac arrest and torsades de pointes have been reported with citalopram although toxicity has occurred in adults ingesting as little as 100–190 mg
- Altered mental state, QT prolongation, bradycardia, syncope, and seizures reported following an overdose of citalopram; fatal outcome in 6 patients with citalopram 840–3920 mg (some had also taken other sedative drugs or alcohol); fatalities reported with overdoses of citalopram and moclobemide when co-prescribed
- Case of serotonin syndrome reported after overdose of 8 g of sertraline
**Management**

- Treatment: Symptomatic and supportive
- Citalopram and escitalopram overdose – asymptomatic patients should have continuous ECG monitoring and monitoring of vital signs for 6 h; symptomatic patients until resolution of symptoms

**Pediatric Considerations**

- For detailed information on the use of SSRIs in this population, please see the *Clinical Handbook of Psychotropic Drugs for Children and Adolescents*[^13]
- No SSRIs are approved for use in pediatric depression in Canada
- Fluoxetine is approved for use in children and adolescents with depression (age 8–17) or OCD (age 7–17) in the USA
- Fluvoxamine and sertraline approved for the treatment of OCD (in children and adolescents > 7 years and > 6 years of age, respectively) (USA)
- Efficacy for major depressive disorder (MDD) in children and adolescents NOT demonstrated in controlled trials with sertraline, paroxetine, and citalopram; no data with fluvoxamine and escitalopram
- CAUTION: Suicidal ideation and attempts (NOT completed suicides) are increased by antidepressants in people under the age of 24 (compared to placebo). No difference seen in those aged 24–65 and a decrease in these phenomena in those over the age of 65
- SSRIs have been used in the treatment of depression, dysthymia, social phobia, anxiety, panic disorder, bulimia, OCD, autism, selective mutism, Tourette’s syndrome, and ADHD; preliminary data suggest efficacy in some children with pervasive developmental disorders (autism) and selective mutism
- Children are more prone to behavioral adverse effects including: Agitation, restlessness (32–46%), activation, hypomania (up to 13%), insomnia (up to 21%), irritability, and social disinhibition (up to 25%)

**Geriatric Considerations**

- SSRIs are used (off-label) in the treatment of behavioral and psychological symptoms of dementia[^14,15]
- SSRIs generally have a low risk of CNS, anticholinergic, and cardiovascular effects
- Initiate lower dose and increase more slowly; higher doses of citalopram have been associated with delirium
- Elderly patients may take longer to respond and may need trials of at least 12 weeks before treatment response noted; data contradictory as to efficacy in older patients
- Half-life of paroxetine increased by 170% and mean plasma level increased 4-fold in the elderly; clearance of sertraline decreased; citalopram plasma level and \( T_{1/2} \) increased; \( C_{\text{max}}, \text{AUC,} \) and \( T_{1/2} \) of escitalopram increased by 35%, 50%, and 50%, respectively
- Limit dose of citalopram and escitalopram to a maximum of 20 mg/day and 10 mg/day, respectively, due to risk of QT prolongation
- Monitor for drug-drug interactions
- Improvement in cognitive functioning in elderly depressed patients has been noted
- Impaired balance and falls reported; tend to occur early in treatment and are more likely with higher doses[^16]
- Both weight gain and weight loss reported; monitor for excessive weight loss in debilitated patients
- Neurological side effects more likely
- Extrapyramidal effects reported; they are not dose related and can develop with short-term or long-term use
- Monitor serum electrolytes (sodium and urea nitrogen levels); hyponatremia reported with all SSRIs (e.g., in 12% of elderly on paroxetine) usually within 2 weeks of drug initiation; can present with confusion, somnolence, fatigue, delirium, hallucinations, urinary incontinence, hypotension, and vomiting

**Use in Pregnancy**

- Increased risk of heart defects (1.5–2%) with paroxetine in early pregnancy, as compared to the general population (1%) – Category D
- AVOID drug
- Fetal echocardiography should be considered for women exposed to paroxetine in early pregnancy (Level B evidence).[^17] Other SSRIs may have similar teratogenic potential, primarily septal defects
- Possible increased risk of miscarriage (Category C drugs); with citalopram, teratogenic effects have been reported in animal studies[^18]
- If possible, avoid SSRIs during first trimester; when stopping the SSRI, taper the dose gradually to minimize adverse fetal outcome; with fluoxetine be aware of long half-life of metabolite, norfluoxetine
- Reports of an increase in premature births and poor neonatal adaptation when drug taken in the third trimester
- Neonates exposed to SSRIs (especially paroxetine) in the third trimester (after 20th week) have developed complications upon delivery including: Jitteriness, restlessness, irritability, tremors, feeding difficulties, changes in muscle tone, respiratory distress, persistent pulmonary hypertension (6-fold risk), temperature instability, seizures (with fluoxetine these are related to blood level of fluoxetine and norfluoxetine)[^19]