

Therapeutic Class Overview

Antidepressants, SSRI

INTRODUCTION

- Major depressive disorder (MDD) is a highly prevalent and disabling disorder characterized by symptoms such as depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (*Simon 2015*).
 - MDD is associated with higher rates of chronic disease, impaired functioning, and increased healthcare utilization. The condition is more prevalent among females and persons aged 40 to 59. From 2009 to 2012, 7.6% of Americans 12 years of age or older had depression (moderate or severe symptoms in the past 2 weeks) (*Pratt and Brody 2014*).
 - Current guidelines recommend first-line treatment with a second-generation antidepressant (SGA) and/or cognitive behavioral therapy (CBT). The effectiveness of SGAs is generally comparable between and within classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). SSRIs, SNRIs, mirtazapine, and bupropion are considered optimal for the treatment of MDD in most patients (*American Psychiatric Association [APA] 2010, Qaseem et al 2016, Veteran's Affairs/Department of Defense [VA/DoD] 2016*).
- SSRIs inhibit the serotonin reuptake pump and increase postsynaptic serotonin receptor occupancy. This initial action may cause subsequent changes involved in treating depression. SSRIs are selective in that they have relatively little affinity for other types of receptors. Reuptake inhibition occurs soon after SSRIs are started, and the full therapeutic effects of SSRIs may not appear for 3 to 8 (or more) weeks after treatment has started (*Hirsch and Birnbaum 2017*).
- Some of the SSRIs are also used to treat other psychiatric disorders besides MDD, including panic disorder, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), social anxiety disorder, posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD)/premenstrual syndrome (PMS), and bulimia nervosa.
 - GAD is characterized by excessive anxiety and worry. Symptoms of GAD include restlessness, being easily fatigued, irritability, difficulty concentrating, muscle tension, and sleep disturbances (*Bandelow et al 2012*).
 - OCD is characterized by recurrent intrusive thoughts, images, or urges (obsessions) that typically cause anxiety or distress, and by repetitive mental or behavioral acts (compulsions) that the individual feels driven to perform, either in response to an obsession or according to rules that he or she believes must be applied rigidly (*Simpson 2016*).
 - Panic disorder is characterized by recurrent unexpected panic attacks followed by concern about subsequent panic attacks or maladaptive change in behavior related to the attacks. Panic attacks are discrete periods of intense fear or discomfort accompanied by somatic and psychic symptoms (eg, palpitations, sweating, trembling, dyspnea, chest pain, nausea) (*APA 2009, Bandelow et al 2012*).
 - PMS is characterized by the presence of both physical and behavioral (including affective) symptoms that occur repetitively in the second half of the menstrual cycle and interfere with some aspects of the woman's life. The APA defines PMDD as a severe form of PMS in which symptoms of anger, irritability, and internal tension are prominent (*Yonkers and Casper 2016*).
 - PTSD is a clinically-significant condition with symptoms that have persisted for more than 1 month after exposure to a traumatic event and caused significant distress or impairment in social, occupational, or other important areas of functioning. PTSD can appear alone as the only diagnosis, or more commonly, with another co-occurring disorder, such as a substance use disorder or mood disorder (*Veterans Affairs [VA]/Department of Defense [DoD] 2017*).
 - Social anxiety disorder is characterized by persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with social anxiety disorder often avoid social interactions or endure them with intense anxiety or distress (*Bandelow et al 2012*).
 - Bulimia nervosa is characterized by recurrent episodes of binge eating and inappropriate compensatory behaviors, as well as frequent comorbid psychopathology (*Engel et al 2017*).
- The scope of this review will be the safety and efficacy of the SSRIs in the treatment of MDD and other psychiatric Food and Drug Administration (FDA)-approved indications. The SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.
 - Brisdelle, a low dose (7.5 mg) paroxetine mesylate formulation, is only FDA-approved for the treatment of moderate to vasomotor symptoms (VMS) associated with menopause. This indication will not be addressed in this review.
- Medispan Therapeutic Class: Selective Serotonin Reuptake Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Brisdelle (paroxetine mesylate) capsules	✓
Celexa (citalopram) oral solution, tablets*	✓
fluoxetine delayed-release (DR) capsules‡	✓
fluoxetine tablets‡	✓
fluvoxamine tablets‡	✓
fluvoxamine ER capsules‡	✓
Lexapro (escitalopram) oral solution, tablets*	✓
Paxil (paroxetine hydrochloride) oral suspension, tablets	✓ †
Paxil CR (paroxetine hydrochloride ER) tablets	✓
Pexeva (paroxetine mesylate) tablets	--
Prozac (fluoxetine) capsules, oral solution*	✓
Sarafem (fluoxetine) capsules‡, tablets	✓
Zoloft (sertraline) oral solution, tablets	✓

*Brand Celexa, Lexapro, and Prozac oral solution are no longer marketed.

†Paxil oral suspension does not have a generic available.

‡Brand Luvox (fluvoxamine) tablets/capsules, Prozac Weekly (fluoxetine) capsules, Prozac (fluoxetine) tablets, and Sarafem (fluoxetine) capsules are no longer marketed.

(Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017)

INDICATIONS

Table 2. FDA Approved Indications for SSRIs

Indication	Citalopram	Escitalopram	Fluoxetine	Fluoxetine (Sarafem)	Fluoxetine DR	Fluvoxamine	Fluvoxamine ER	Paroxetine hydrochloride	Paroxetine hydrochloride ER	Paroxetine mesylate (Brisdelle)	Paroxetine mesylate (Pexeva)	Sertraline
GAD		✓						✓			✓	
MDD	✓	✓	✓		✓			✓	✓		✓	✓
OCD			✓			✓	✓	✓			✓	✓
Moderate to VMS associated with menopause										✓		
Panic disorder			✓					✓	✓		✓	✓
PMDD				✓					✓			✓
PTSD								✓				✓
Social anxiety disorder								✓	✓			✓
Bulimia nervosa			✓									

(Prescribing information: Brisdelle 2017, Celexa tablets 2017, citalopram oral solution 2017, fluoxetine delayed-release 2015, fluoxetine tablets 2016, fluvoxamine 2017, fluvoxamine extended-release 2015, Lexapro 2017, Paxil 2016, Paxil CR 2016, Pexeva 2017; Prozac 2017, Sarafem 2017, Zoloft 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

GAD

- There is a lack of data available directly comparing different serotonergic reuptake inhibitors (including SSRIs vs SNRIs) for GAD. Trials have generally shown that all serotonergic reuptake inhibitors studied have the same degree of effectiveness, ie, response rates of approximately 60 to 70% for the serotonergic reuptake inhibitors vs. 40% for the placebo. SSRIs that have been shown in randomized control trials (RCTs) to be efficacious for GAD include paroxetine, sertraline, citalopram, and escitalopram. Uncontrolled trials and our clinical experience suggest other SSRIs (eg, fluoxetine and fluvoxamine) are effective for GAD as well (*Bystritsky 2016*).

MDD

- A large body of literature supports the superiority of SSRIs compared with placebo in the treatment of MDD. Although a few analyses suggest small advantages of SNRIs over SSRIs in rates of remission, a preponderance of the data finds no significant evidence of the superiority of any other class or agents over SSRIs. Most individual trials and meta-analyses show no differences in efficacy among individual SSRIs (*APA 2010, VA/DoD 2016*).
- A 2011 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review evaluated bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine in the treatment of adults with depressive disorders (*Gartlehner et al 2011*).

- Overall, treatment effects were similar among SGAs. Some analyses yielded statistically significant differences among treatments, but the magnitudes of differences were modest and probably not clinically relevant.
 - Meta-analyses of head-to-head trials showed statistically significantly greater response rates for escitalopram than citalopram (1 unpublished study and 5 published studies involving 1802 patients) (odds ratio [OR], 1.49, 95% confidence interval [CI], 1.07 to 2.01), and sertraline than fluoxetine (4 studies involving 960 patients) (OR, 1.42, 95% CI, 1.08 to 1.85).
- In several head-to-head trials, overall efficacy in maintaining remission did not significantly differ between escitalopram and desvenlafaxine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine.
- For patients with MDD and accompanying anxiety, 4 head-to-head trials suggested that antidepressants have similar antidepressive efficacy. Two of these studies compared SSRIs (fluoxetine, paroxetine, and sertraline).
- Overall, SGAs caused similar adverse events (AEs); however, the frequency of specific events differed among some drugs. In addition, Discontinuation rates were similar between SSRIs and other SGAs (range of means, 15% to 25%).
- A multiple-treatments meta-analysis of 117 RCTs (n = 25,928) found clinically important differences when comparing bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine (not approved in the United States), sertraline, and venlafaxine for the acute treatment of adults with MDD. (*Cipriani et al 2009*).
 - Patients on mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more likely to respond to therapy than those on duloxetine (OR 1.39, 1.33, 1.30 and 1.27, respectively), fluoxetine (OR 1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (OR 1.41, 1.35, 1.30, and 1.27, respectively), and paroxetine (OR 1.35, 1.30, 1.27, and 1.22, respectively).
 - Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, and venlafaxine.

OCD

- A Cochrane review of 17 RCT and quasi RCT studies (n = 3097) evaluated the efficacy and AEs of SSRIs vs placebo for OCD in adults. SSRIs as a group were more effective than placebo in reducing the symptoms of OCD between 6 and 13 weeks post-treatment, measured using the Yale-Brown Obsessive Compulsive Scale (YBOCS) (weighted mean difference [WMD] -3.21, 95% CI -3.84 to -2.57). The WMD for individual SSRI drugs were similar and not statistically different. Based on 13 studies (2697 participants), SSRIs were more effective than placebo in achieving clinical response at post-treatment (relative risk [RR] 1.84, 95% CI 1.56 to 2.17). The pooled RR was shown to be similar between individual SSRI drugs. Although reported AEs data were more limited, with few exceptions, the overall and individual AEs for the different SSRIs were always worse than for placebo and, in the majority of cases, the difference was statistically significant. Nausea, headache and insomnia were always reported amongst the most common AEs in clinical trials for each of the drugs (*Soomro et al 2008*).

Panic Disorder

- A Cochrane review of 35 RCTs (n = 6785) evaluated antidepressants and benzodiazepines as monotherapy for adults with panic disorder. An analysis of 2 studies (n = 1316) directly comparing paroxetine with venlafaxine demonstrated similar response rates for panic disorder (RR 0.96; 95% CI, 0.75 to 1.23; 2 studies; 991 participants; I² = 1%; high quality of evidence). Additionally, no difference in response rate was detected between antidepressants and benzodiazepines for panic disorder (RR 0.99; 95% CI, 0.67 to 1.47; 2 studies; 215 participants; low quality of evidence) (*Bighelli et al 2016*).
- In a meta-analysis of 50 studies (n = 5236) of antidepressants for panic disorder, the following antidepressants demonstrated superiority over placebo in the reduction from baseline of overall anxiety symptoms (in increasing order of effectiveness): citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine (*Andrisano et al 2013*).

PMDD

- A Cochrane review of 31 RCTs (n = 6785) evaluated the effectiveness and safety of SSRIs for treating PMS. The review compared fluoxetine, paroxetine, sertraline, escitalopram and citalopram vs. placebo. SSRIs reduced overall self-rated symptoms significantly more effectively than placebo. The effect size was moderate when studies reporting end scores were pooled (for moderate dose SSRIs: SMD -0.65, 95% CI -0.46 to -0.84; n = 9 studies, 1276 women; moderate heterogeneity I² = 58%; low quality evidence). SSRIs were effective for symptom relief whether taken only in the luteal

phase or continuously, with no clear evidence of a difference in effectiveness between these modes of administration. However, few studies directly compared luteal and continuous regimens and more evidence is needed on this question. Withdrawals due to AEs were significantly more likely to occur in the SSRI group. In secondary analyses, SSRIs were effective for treating specific types of symptoms (eg, psychological, physical and functional symptoms, and irritability) (*Marjoribanks et al 2013*).

PTSD

- A systematic review and meta-analysis of RCTs ($n = 51$ studies) evaluated the efficacy of all types of pharmacotherapy, as monotherapy, in reducing symptoms of PTSD. SSRIs were found to be statistically superior to placebo in reduction of PTSD symptoms but the effect size was small (standardized mean difference -0.23 , 95% CI -0.33 to -0.12). Three drugs were significantly superior to placebo on either clinician- and self-rated PTSD symptom severity combined (paroxetine) or clinician-rated PTSD symptom severity alone (fluoxetine and venlafaxine). Insufficient evidence was found to support the preferential use of individual agents in either combat-related or non-combat-related trauma (*Hoskins et al 2015*).

Social Anxiety Disorder

- A systematic review and meta-analysis of RCTs (41 studies) aimed to identify optimal treatments for social phobia (ie, social anxiety disorder) (*Canton et al 2012*).
 - SSRIs were the most extensively tested in patients with social phobia, with 17 placebo-controlled acute treatment RCTs reported. Almost half of the studies studied paroxetine, with 2 to 3 studies each for escitalopram, fluoxetine, fluvoxamine, and sertraline. The pooled OR for response to each SSRI ranged between 1.98 (95% CI, 1.07 to 3.67) for fluoxetine and 3.41 (95% CI, 2.51 to 4.69) for paroxetine. The overall OR was 2.73 (95% CI, 1.67 to 4.48). With 1 exception, SSRIs had significantly greater Clinical Global Impressions (CGI) response rates compared with placebo.
 - In general, SSRIs showed separation from placebo by weeks 4 to 6 on a number of response or other outcome measures; however SSRI-placebo differences tended to increase out to 12 weeks of treatment.
 - There have been 4 studies assessing the effect of continuation treatment with SSRIs in patients who have responded to acute treatment. In these relapse prevention studies, patients were randomized to remain on their SSRI or were switched to placebo, under double-blind conditions. All 4 studies showed robust effects of the SSRIs in preventing relapse of social phobia (pooled OR 0.25, 95% CI, 0.18 to 0.35).

CLINICAL GUIDELINES

GAD

- **World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care** (*Bandelow et al 2012*)
 - The first-line pharmacologic therapies for GAD are SSRIs, SNRIs and pregabalin. Other treatment options include buspirone and hydroxyzine. Benzodiazepines should only be used for long-term treatment when other drugs or CBT have failed.

MDD

- **VA/DoD Clinical Practice Guideline for the Management of MDD** (*VA/DoD 2016*)
 - As first-line treatment for uncomplicated mild to moderate MDD, evidence-based psychotherapy or evidence-based pharmacotherapy should be offered. Selection should be based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication, and provider training/competence.
 - Evidence-based pharmacotherapy includes SSRIs (except fluvoxamine), SNRIs, mirtazapine, and bupropion.
 - The evidence does not support recommending a specific psychotherapy or pharmacotherapy over another.
 - In patients who have demonstrated partial or no response to initial maximized monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy is recommended.
 - In cases of severe MDD, combined pharmacotherapy and psychotherapy is recommended if initial monotherapy with an antidepressant did not achieve a response or remission. In patients who have demonstrated a partial response and are tolerating the current antidepressant, augmentation with another medication or psychotherapy is reasonable.

- **Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With MDD: A Clinical Practice Guideline From the American College of Physicians (ACP)** (*Qaseem et al 2016*)
 - Clinicians are recommended to select between either cognitive behavioral therapy or SGAs (SSRIs, SNRIs) to treat patients with MDD after discussing treatment effects, AE profiles, cost, accessibility, and preferences with the patient (Grade: Strong recommendation, moderate-quality evidence).
 - There are reported differences among SGAs in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) AEs. Bupropion is associated with a lower rate of sexual AEs than fluoxetine and sertraline, whereas paroxetine has higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, and sertraline. Physicians and patients should discuss AE profiles before selecting a medication.
- **American Psychiatric Association (APA) Practice Guideline for the Treatment of MDD: 3rd Edition** (*APA 2010*)
 - The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference.
 - For most patients, an SSRI, an SNRI, mirtazapine, or bupropion is optimal. In general, the use of MAOIs should be restricted to patients who do not respond to other treatments.

OCD

- **APA Practice Guideline for the Treatment of OCD** (*APA 2013*)
 - The guideline recommends CBT or a serotonin reuptake inhibitor (ie, SSRIs or clomipramine) as first-line treatments for OCD. Choice of treatment modality depends on many factors, including the nature and severity of the patient's symptoms, the nature of any co-occurring psychiatric and medical conditions and their treatments, the availability of CBT, and the patient's past treatment history, current medications, and preferences.
 - The guideline notes that all SSRIs appear to be equally effective in treating OCD, even though citalopram and escitalopram are not FDA-approved for this indication.
 - The guideline notes the importance, when selecting among the SSRIs, of considering the safety and acceptability of particular side effects for a given patient. Paroxetine was noted to be the SSRI most associated with weight gain.

Panic Disorder

- **WFSBP Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care** (*Bandelow et al 2012*)
 - In acute panic attacks, reassurance of the patient may be sufficient in most cases. In severe attacks, short-acting benzodiazepines may be needed (eg, melting tablets). SSRIs and venlafaxine are the first-line treatments for panic disorder. After remission, treatment should continue for at least several months in order to prevent relapses. SSRIs, venlafaxine, TCAs, benzodiazepines and other drugs have shown long-term efficacy in these studies.
- **APA Practice Guideline for the Treatment of Panic Disorder** (*APA 2009*)
 - The use of a SSRI, SNRI, TCA, or CBT as the initial treatment for panic disorder is strongly supported by demonstrated efficacy in numerous RCTs. In the absence of a co-occurring mood disorder, monotherapy with a benzodiazepine is also an appropriate initial treatment.
 - The relatively favorable safety and side-effect profile of SSRIs and SNRIs makes them the best initial pharmacotherapy choice for many patients with panic disorder.
 - A particular form of psychodynamic psychotherapy, panic-focused psychodynamic psychotherapy (PFPP), was effective in 1 RCT and could be offered as an initial treatment.
 - There is insufficient evidence to recommend any of these pharmacological or psychosocial interventions as superior to another, or to routinely recommend a combination of treatments over monotherapy, although a combination may be chosen based on individual circumstances.

PMDD

- **American Family Physician – PMS and PMDD** (*Hofmeister and Bodden 2016*)
 - SSRIs are first-line treatment for severe symptoms of PMS and PMDD. Sertraline, paroxetine, fluoxetine, citalopram, and escitalopram can be used to treat the psychiatric symptoms of PMS and PMDD and have been shown to relieve some of the physical symptoms.

- A 2013 Cochrane review analyzed 31 RCTs that compared SSRIs with placebo for symptom relief of PMS. Each of the 5 SSRIs studied had statistically significant benefits on patient-reported symptoms when taken continuously or only during the luteal phase, but more direct studies comparing luteal phase administration with continuous administration are needed.
- SNRIs such as venlafaxine have been used off-label to treat PMDD in women with predominantly psychological symptoms. The effect is achieved over a relatively short period, 3 to 4 weeks, and sustained throughout subsequent menstrual cycles.

PTSD

- **VA/DoD Clinical Practice Guideline for the Management of PTSD (VA/DoD 2017)**
 - For those patients who choose not to engage in or are unable to access trauma-focused psychotherapy, the use of sertraline, paroxetine, fluoxetine, or venlafaxine as monotherapy is recommended based on the results of 3 systematic reviews. Each of these 3 meta-analyses concluded that sertraline, paroxetine, fluoxetine, and venlafaxine each had stronger evidence to support use in the treatment of PTSD compared to the other SSRIs and SNRIs. The benefits of these medications also outweigh the potential harms.
- **APA Practice Guideline for the Treatment of Acute Stress Disorder and PTSD (APA 2004, APA 2009 [update])**
 - The 2004 guideline recommended the SSRIs as a first-line medication treatment for patients with PTSD. The trials reviewed in the 2009 update suggest that the SSRIs may no longer be recommended with the same level of confidence for veterans with combat-related PTSD as for patients with non-combat-related PTSD. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment.
 - No significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available.

Social Anxiety Disorder

- **WFSBP Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care (Bandelow et al 2012)**
 - The guideline recommends SSRIs and venlafaxine for first-line pharmacologic therapy for social anxiety disorder. There is insufficient evidence to recommend benzodiazepines or TCAs. Exposure therapy and CBT are also effective psychotherapies.

Bulimia Nervosa

- **APA Practice Guideline for the Treatment of Eating Disorders (APA 2012)**
 - In a 2011 systematic review for the WFSBP, *Aigner et al* identified 36 RCTs of medications for the treatment of bulimia nervosa. They reported that for TCA, Grade A evidence exists with a moderate risk-benefit ratio. For fluoxetine, Grade A evidence exists with a good risk-benefit ratio, and for topiramate, there is Grade A evidence with a moderate risk-benefit ratio. These findings and recommendations were consistent with the 2006 APA guideline, which recommends antidepressants, particularly the SSRIs, as one effective component of the initial treatment program for most patients with bulimia nervosa.
 - Other pharmaceutical agents, including oxcarbazepine, aripiprazole, and baclofen, have been reported to be effective for bulimia nervosa, but the results were from small case series or studies sponsored by the drug manufacturer.
 - Citalopram was studied in a small single-blind 12-week RCT. In this study, 37 patients with bulimia nervosa received fluoxetine (20 to 60 mg/day) or citalopram (20 to 40 mg/day). Both groups improved with respect to eating pathology. Patients receiving fluoxetine reported greater reductions in introjected anger, whereas those receiving citalopram reported greater reduction in depressive feelings.

SAFETY SUMMARY

- SSRIs are contraindicated in patients receiving MAOIs or within 14 days of their discontinuation.
- All SSRIs carry a boxed warning for suicidal thoughts and behaviors. The risk of suicidal thinking and behavior is increased in children, adolescents, and young adults taking SSRIs.
- The use of SSRIs with other serotonergic agent increases the likelihood of serotonergic AEs and should be monitored closely. Drugs that have serotonergic properties include meperidine, triptans, most antidepressants, amphetamines, ergot alkaloids, dopamine antagonists, St. John's wort, and others. Additionally, SSRIs should not be administered with an SNRI or another SSRI as the risk for serotonin syndrome or neuroleptic malignant syndrome is greatly increased.

- The SSRIs tend to have similar side effect profiles; however, certain SSRIs may be more likely to cause specific side effects. Thus, some patients who cannot tolerate one SSRI may do well with another. Common AEs are summarized in the table below (*Hirsch and Birnbaum 2017*).

Table 3. AEs of SSRIs

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity [†]	Weight gain	Sexual dysfunction
Citalopram	0	0	1+	1+	1+ ^Δ	1+	1+	3+
Escitalopram	0	0	1+	1+	1+	1+	1+	3+
Fluoxetine	0	0	2+	1+	1+	1+	1+	3+
Fluvoxamine	0	1+	1+	1+	0 to 1+	1+	1+	3+
Paroxetine	1+	1+	1+	2+	0 to 1+	1+	2+	4+
Sertraline	0	0	2+	1+	0 to 1+	2+ [◇]	1+	3+

* Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects.

[†] All SSRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.

^Δ Based upon reports of dose related QTc prolongation and arrhythmia, the maximum recommended dose of citalopram is 20 mg for patients at increased risk of elevated citalopram serum concentrations.

[◇] Sertraline is associated with higher rates of diarrhea.

DOSing AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Brisdelle (paroxetine mesylate)	Capsules	Oral	Once daily at bedtime	--
Celexa (citalopram)	Oral solution, tablets	Oral	Once daily, in the morning or evening	<ul style="list-style-type: none"> • Dosing adjustment in hepatic impairment; use with caution in severe renal impairment
fluoxetine DR	Capsules	Oral	Once weekly	<ul style="list-style-type: none"> • Initiate fluoxetine DR capsules 7 days after the last daily dose of fluoxetine 20 mg • Dosing adjustment in hepatic impairment
Fluvoxamine	ER capsules, tablets	Oral	Capsules: once daily at bedtime Tablets: once daily at bedtime for total daily doses ≤ 50 mg (pediatric) or ≤ 100 mg (adults); divided in 2 doses for total daily doses > 50 mg (pediatric) or > 100 mg (adults)	<ul style="list-style-type: none"> • Dosing adjustment in hepatic impairment
Lexapro (escitalopram)	Oral solution, tablets	Oral	Once daily, in the morning or evening	<ul style="list-style-type: none"> • Dosing adjustment in hepatic impairment; use

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				with caution in severe renal impairment
Paxil (paroxetine hydrochloride)	Oral suspension, tablets	Oral	Once daily, usually in the morning	<ul style="list-style-type: none"> Dosing adjustment in renal or hepatic impairment
Paxil CR (paroxetine hydrochloride)	Tablets	Oral	Once daily, usually in the morning	<ul style="list-style-type: none"> Dosing adjustment in renal or hepatic impairment
Pexeva (paroxetine mesylate)	Tablets	Oral	Once daily, usually in the morning	<ul style="list-style-type: none"> Dosing adjustment in severe renal or hepatic impairment
Prozac (fluoxetine)	Capsules, oral solution, tablets	Oral	Once daily, in the morning or twice a day	<ul style="list-style-type: none"> Dosing adjustment in hepatic impairment
Sarafem (fluoxetine)	Capsules, tablets	Oral	Once daily, given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle)	<ul style="list-style-type: none"> Dosing adjustment in hepatic impairment
Zoloft (sertraline)	Oral solution, tablets	Oral	Once daily	<ul style="list-style-type: none"> Dosing adjustment in mild hepatic impairment; not recommended in moderate to severe hepatic impairment

See the current prescribing information for full details

CONCLUSION

- SSRIs are frequently used as first-line antidepressants because of their efficacy, tolerability, and general safety in overdose.
- According to clinical practice guidelines, CBT and SGAs are equally effective first-line monotherapies in the initial treatment of patients with MDD. There is insufficient evidence to recommend a specific psychotherapy or pharmacotherapy over another. The effectiveness is generally comparable between classes and within classes of SGAs. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference (*APA 2010, Qaseem et al 2016, VA/DoD 2016*).
- Some of the SSRIs are also FDA-approved to treat other psychiatric disorders besides MDD, including panic disorder, OCD, GAD, social anxiety disorder, PTSD, PMDD, and bulimia nervosa. For these various indications, there are generally no significant differences among the SSRIs; however, some products do have a stronger level of evidence or more clinical data available.
- The SSRIs tend to have similar side effect profiles; however, certain SSRIs may be more likely to cause specific side effects. Thus, some patients who cannot tolerate 1 SSRI may do well with another. AEs include: drowsiness, insomnia, QTc prolongation, orthostatic hypotension, weight gain, and sexual dysfunction.
- All SSRIs carry a boxed warning for suicidal thoughts and behaviors, with an increased risk in children, adolescents, and young adults taking SSRIs. The use of SSRIs with other serotonergic agent increases the likelihood of serotonergic AEs and should be monitored closely.

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