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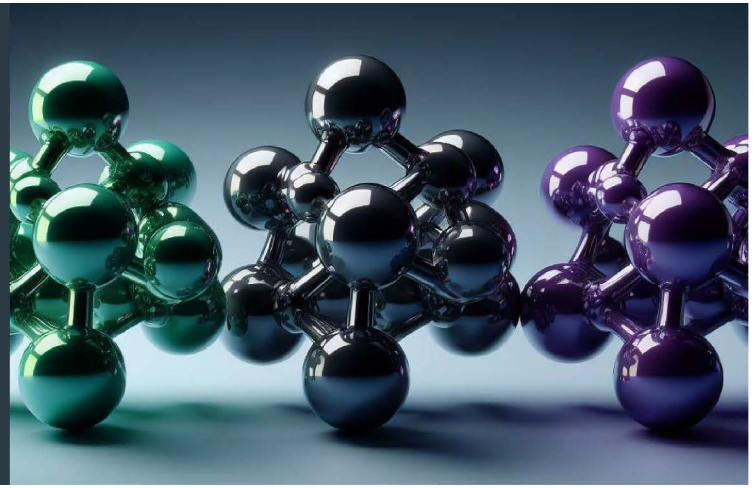
Therapeutic Class Review



ANTIDEPRESSANTS, SSRIs

Client Name: TX HHSC
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The attached document provides a thorough review of the Antidepressants, SSRIs class of medications, detailing their pharmacologic properties, clinical efficacy, safety profiles, and associated therapeutic considerations. This review aims to support healthcare professionals, payers, and other stakeholders in making informed decisions regarding the use of these medications in clinical practice.

Revision History

Date	Version	Revisions
11/1/2023	V1	TCR created GWT updates (highlighted portions are new drug information and updates since the last therapeutic drug class review by the state of Texas DUR Board based on Gainwell's resources/reference materials): • Added escitalopram indication for GAD in pediatric patients. • Omitted Pexeva (off-market). • Added literature reviews on GAD and Panic Disorder (Strawn et al., 2023; Chawla et al., 2022). • Updated guidelines for GAD (WFSBP 2023), MDD (ACP 2023), OCD (WFSBP 2023), Panic Disorder (WFSBP 2023), PTSD (WFSBP 2023), Social Anxiety Disorder (WFSBP 2023), and recommendations spanning multiple indications for perinatal antidepressant use (ACOG 2023). • Added guidelines for bulimia nervosa (APA 2023), MDD (VA/DoD 2022), PTSD (VA/DoD 2023), and VMS (NAMS 2023).

Executive Summary[1-19]

Major depressive disorder (MDD) is a highly prevalent mental health condition characterized by persistent depressive symptoms that produce distress or functional impairment and cannot be attributed to another medical or psychiatric disorder. The management of MDD may involve psychotherapy (e.g., cognitive behavioral therapy), pharmacotherapy, or both, with a choice of modality driven by patient preference and other patient-specific considerations.

This review focuses on the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in the treatment of MDD and other related disorders. SSRIs have become the mainstay of initial pharmacologic therapy for MDD due to their efficacy and relatively favorable side effect profile. These second-generation antidepressants are also employed in the management of a range of other mental health conditions, including anxiety disorders, obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), and non-mental health disorders like pain disorders and vasomotor symptoms of menopause (VMS).

The SSRIs commonly used include escitalopram, fluoxetine, paroxetine, and sertraline. Most agents in this class are available generically and come in multiple oral formulations, making them accessible for diverse patient needs. Escitalopram and fluoxetine are notable for their pediatric indications in treating MDD, with fluoxetine also available as a once-weekly delayed-release capsule for adult MDD treatment. A boxed warning is present for all SSRIs regarding the potential for increased risk of suicidal ideation in adolescents and young adults, underscoring the need for careful patient monitoring.

In terms of individual agent specifics, immediate-release fluoxetine is distinct for its labeled use in treating binge-eating and vomiting behaviors in bulimia nervosa. In contrast, escitalopram and immediate-release paroxetine are approved for generalized anxiety disorder (GAD), with escitalopram also indicated for certain pediatric patients with GAD. For OCD treatment, immediate-release fluoxetine, fluvoxamine, paroxetine (except the 7.5 mg capsules), and sertraline are recommended as first-line therapies, mirroring their use in panic disorder and PTSD. Sertraline and both immediate- and extended-release paroxetine formulations are recommended for social anxiety disorder, with paroxetine 7.5 mg capsules specifically labeled for vasomotor symptoms of menopause.

Selecting an SSRI involves considering the agent's side effect profile, potential drug interactions, and patient-specific factors such as existing comorbidities and concurrent medications. While all SSRIs are generally regarded as adequate for MDD and other indicated disorders, individual response can vary, making personalized treatment important. Recent comparative data to guide selection among SSRIs or other antidepressant classes for MDD are limited, highlighting the importance of clinical judgment and patient preference in therapeutic decisions.

The selection of agents for inclusion on the Preferred Drug List should account for differences in labeled indications (including unique subpopulations), guideline-recommended uses, the potential need to switch agents within or between mechanistic classes (e.g., due to efficacy, toxicity, or drug interactions), differences in available formulations, and patient, caregiver, and clinician preferences.

Drug (Route of Administration)	Indications								
	Bulimia Nervosa	GAD	MDD	OCD	Panic disorder	PMDD	PTSD	Social Anxiety Disorder	VMS
Citalopram Celexa®[G] (PO)	--	--	x	--	--	--	--	--	--
Escitalopram Lexapro®[G] (PO)	--	x*	x**	--	--	--	--	--	--
Fluoxetine Fluoxetine weekly DR† (PO)	--	--	x‡	--	--	--	--	--	--
Prozac® IR[G§] (PO)	x	--	x‡	x£	x	x	--	--	--
Fluvoxamine Fluvoxamine IR† (PO)	--	--	--	x‡	--	--	--	--	--
Fluvoxamine ER† (PO)	--	--	--	x	--	--	--	--	--
Paroxetine Brisdelle® IR[G] (PO)	--	--	--	--	--	--	--	--	x
Paxil® IR[G] (PO)	--	x	x	x	x	--	x	x	--
Paxil CR®[G] (PO)	--	--	x	--	x	x	--	x	--
Sertraline Zoloft®[G€] (PO)	--	--	x	x¥	x	x	x	x	--

[G]*Available generically*
**Adults (all formulations) and pediatric patients aged ≥7 years (brand-name only)*
***Adults and pediatric patients aged ≥12 years*
†*Only available generically*
‡*Adults and pediatric patients aged ≥8 years*
§*Fluoxetine products labeled for PMDD are not labeled for non-PMDD indications and vice versa*
£*Adults and pediatric patients aged ≥7 years*
¥*Adults and pediatric patients aged ≥6 years*
€*Sertraline capsules are only labeled for MDD and OCD as continuation of therapy following initiation with lower-strength dosage forms*
Abbreviations: DR, delayed release; ER, extended release; GAD, generalized anxiety disorder; IR, immediate release; MDD, major depressive disorder; OCD, obsessive compulsive disorder; PMDD, premenstrual dysphoric disorder; PO, orally; PTSD, posttraumatic stress disorder; VMS, vasomotor symptoms of menopause.

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Table 1. Antidepressants, SSRIs, Class Characteristics[1,2,4]

Mechanism of Action	Selectively inhibit reuptake of serotonin at the presynaptic membrane, which increases serotonin concentrations in the neuronal synapse and produces downregulation of serotonin autoreceptors, leading to increased serotonin neurotransmitter activity.
Contraindications	Concomitant MAOIs or pimozide
Significant Warnings	• **Boxed warning**: Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. • Activation of mania/hypomania • Angle-closure glaucoma • Bleeding risk • Discontinuation syndrome • Seizure risk • Serotonin syndrome • Sexual dysfunction • SIADH
Significant Adverse Events	Diarrhea, insomnia, nausea

Abbreviations: MAOI, monoamine oxidase inhibitor; SIADH, syndrome of inappropriate antidiuretic hormone.

Table 2. Antidepressants, SSRIs, Differentiating Characteristics[1,2]

Generic Name (Brand Name) Manufacturer	Approved Indications	Distinguishing Features	Dosage and Administration	How Supplied	Generic Availability
Citalopram (Celexa®) Various	• MDD in adults	Serious warnings • QT prolongation Other • May require dosage adjustment when used with CYP2C19 inhibitors	MDD • 20 mg PO once daily (titrate as indicated)	• Capsules: 30 mg • Oral solution: 10 mg/5 mL • Tablets: 10 mg, 20 mg, 40 mg	• Citalopram capsules • Citalopram oral solution • Citalopram tablets
Escitalopram (Lexapro®) Various	• GAD in adults (all formulations) and pediatric patients aged ≥7 years (brand-name only) • MDD in adults and pediatric patients aged ≥12 years	None	GAD • All age groups: 10 mg PO once daily (titrate as indicated) MDD • All age groups: 10 mg PO once daily (titrate as indicated)	• Oral solution: 1 mg/mL • Tablets: 5 mg, 10 mg, 20 mg	• Escitalopram oral solution • Escitalopram tablets
Fluoxetine* (Prozac®) Various	• Binge-eating and vomiting behaviors in adults with moderate to severe bulimia nervosa • MDD in adults and pediatric patients aged ≥8 years • OCD in adults and pediatric patients aged ≥7 years • Panic disorder in adults • PMDD in adults	Contraindications • Concomitant thioridazine Serious warnings • Anorexia/weight loss • Rash/urticaria • QT prolongation	Bulimia nervosa • 60 mg PO once daily MDD • Adults: 20 mg PO once daily (titrate as indicated) • Pediatric patients: 10 to 20 mg PO once daily (titrate as indicated) • All age groups (weekly DR capsules only): 90 mg PO once weekly (equivalent to 20 mg PO once daily)	• Capsules: 10 mg, 20 mg, 40 mg • Weekly DR capsules: 90 mg • Oral solution: 20 mg/5 mL • Tablets: 10 mg, 20 mg, 60 mg	• Fluoxetine capsules • Fluoxetine weekly DR capsules • Fluoxetine oral solution • Fluoxetine tablets

Generic Name (Brand Name) Manufacturer	Approved Indications	Distinguishing Features	Dosage and Administration	How Supplied	Generic Availability
			OCD • Adults: 20 mg PO once daily (titrate as indicated) • Pediatric patients: 10 mg PO once daily (titrate as indicated) Panic disorder • 10 mg PO once daily (titrate as indicated) PMDD • 20 mg PO once daily on a continuous or intermittent basis (titrate as indicated)		
Fluvoxamine (Luvox®**) Various	• OCD in adults (IR and ER formulations) and pediatric patients aged ≥8 years (IR formulations only)	Contraindications • All formulations: Concomitant thioridazine, tizanidine, or alosetron • ER formulations: Concomitant ramelteon	OCD • Adults: 50 mg PO (IR formulations) or 100 mg PO (ER formulations) once daily (titrate as indicated) • Pediatric patients: 25 mg PO once daily (titrate as indicated)	• IR tablets: 25 mg, 50 mg, 100 mg • ER capsules: 100 mg, 150 mg	• Fluvoxamine IR tablets • Fluvoxamine ER capsules
Paroxetine IR (Paxil®) Various (Brisdelle® 7.5 mg capsules) Various	• GAD in adults • MDD in adults • OCD in adults • Panic disorder in adults • PTSD in adults • Social anxiety disorder in adults • Moderate to severe VMS (7.5 mg capsules only)	Contraindications • Concomitant thioridazine Serious warnings • Concomitant tamoxifen • Risk of fetal harm Other • Strong CYP2D6 inhibitor	GAD • 20 mg PO once daily (titrate as indicated) MDD • 20 mg PO once daily (titrate as indicated) OCD • 20 mg PO once daily (titrate as indicated) Panic disorder • 10 mg PO once daily (titrate as indicated) PTSD • 20 mg PO once daily (titrate as indicated) Social anxiety disorder • 20 mg PO once daily (titrate as indicated) VMS • 7.5 mg PO once daily	• IR capsules: 7.5 mg • IR tablets: 10 mg, 20 mg, 30 mg, 40 mg • Oral solution: 10 mg/5 mL	• Paclitaxel IR capsules • Paclitaxel IR tablets • Paclitaxel oral solution
Paroxetine ER (Paxil CR®) Various	• MDD in adults • Panic disorder in adults • PMDD in adults	Contraindications • Concomitant thioridazine Serious warnings	MDD • 25 mg PO once daily (titrate as indicated)	• ER tablets: 12.5 mg, 25 mg, 37.5 mg	• Paclitaxel ER tablets

Generic Name (Brand Name) Manufacturer	Approved Indications	Distinguishing Features	Dosage and Administration	How Supplied	Generic Availability
	• Social anxiety disorder in adults	• Concomitant tamoxifen • Risk of fetal harm Other Strong CYP2D6 inhibitor	Panic disorder • 12.5 mg PO once daily (titrate as indicated) PMDD • 12.5 mg PO once daily (titrate as indicated) Social anxiety disorder • 12.5 mg PO once daily (titrate as indicated)		
Sertraline (Zoloft®) Various	• MDD in adults (all formulations) • OCD in adults and pediatric patients aged ≥6 years (all formulations) • Panic disorder in adults (tablets, oral solution) • PMDD in adults (tablets, oral solution) • PTSD in adults (tablets, oral solution) • Social anxiety disorder in adults (tablets, oral solution)	Contraindications • Oral solution: Concomitant disulfiram Serious warnings • False-positive BZD urine screening tests Other • Oral solution contains alcohol	MDD • 50 mg PO once daily (titrate as indicated) OCD • Adults and pediatric patients aged 13 to 17 years: 50 mg PO once daily (titrate as indicated) • Pediatric patients aged 6 to 12 years: 25 mg PO once daily (titrate as indicated) Panic disorder • 25 mg PO once daily (titrate as indicated) PMDD • 25 mg PO once daily (titrate as indicated) PTSD • 25 mg PO once daily (titrate as indicated) Social anxiety disorder • 25 mg PO once daily (titrate as indicated)	• Capsules: 150 mg, 200 mg • Oral solution: 20 mg/mL • Tablets: 25 mg, 50 mg, 100 mg	• Sertraline capsules • Sertraline oral solution • Sertraline tablets

**Fluoxetine products labeled for PMDD are not labeled for non-PMDD indications and vice versa. Fluoxetine weekly DR capsules are only labeled for MDD.*
***Off-market*
Abbreviations: BZD, benzodiazepine; DR, delayed release; ER, extended release; GAD, generalized anxiety disorder; IR, immediate release; MDD, major depressive disorder; OCD, obsessive compulsive disorder; PMDD, premenstrual dysphoric disorder; PO, orally; PTSD, posttraumatic stress disorder; VMS, vasomotor symptoms of menopause.

Relevant Clinical Trial Data[5]

Generalized Anxiety Disorder

- Escitalopram was evaluated for treating GAD in pediatric patients aged ≥7 years in a randomized, double-blind, multicenter trial (Strawn et al., 2023). Patients with a Pediatric Anxiety Rating Scale for GAD (PARS-GAD) score ≥15 and a Clinical Global Impression of Severity score ≥4 were randomized to receive escitalopram 10 mg PO once daily (with the option to titrate to 20 mg PO once daily) or placebo for eight weeks. The primary outcome was change in PARS-GAD score from baseline to week 8. Among 275 randomized patients, the mean age was 12.6 years; most patients (67%) were 12 to 17 years old. Least-squares mean change in PARS-GAD score from baseline to week eight was significantly improved in patients assigned to escitalopram compared with those assigned to placebo (between-group difference, -1.42; 95% confidence interval [CI], -2.69 to -0.15; p=0.0281). Treatment-emergent adverse events were reported more commonly in the escitalopram group, with the most common events including nausea (13.1% of escitalopram recipients vs 4.4% of placebo recipients), decreased appetite (6.6% vs 2.2%), insomnia (5.1% vs. 1.5%), and somnolence (5.1% vs. 1.5%).

Class Comparative Trial Data[6,7]

Panic Disorder

- A systematic review with network meta-analysis compared pharmacologic therapies for panic disorder with or without agoraphobia (Chawla et al., 2022). Based on the surface under the cumulative ranking curve, benzodiazepines (84.5%), tricyclic antidepressants (68.7%), and selective serotonin reuptake inhibitors (SSRIs) (66.4%) had the highest probability of being the best treatments for inducing remission. Among these classes, the risk ratio (RR) for experiencing an adverse event was lowest for SSRIs (RR 1.19; 95% CI, 1.01 to 1.41).
- A systematic review with meta-analysis compared adverse events reported with antidepressant use in randomized trials or observational studies of older patients with MDD (Sobieraj et al., 2019). Overall adverse event rates reported with serotonin and norepinephrine reuptake inhibitors (SNRIs) were significantly greater than with placebo (RR 1.14; 95% CI, 1.03 to 1.25), whereas no significant difference was identified with SSRIs compared with placebo or SNRIs (pooled analysis values not reported). SSRIs were associated with a lower risk of adverse events than tricyclic antidepressants (RR 0.71; 95% CI, 0.5 to 0.99).

Special Population Considerations[1,2]

Pediatric

- Safety and effectiveness of citalopram, fluvoxamine extended-release, and paroxetine have not been established in pediatric patients.
- Escitalopram: Safety and effectiveness have been established for treating GAD in pediatric patients aged ≥7 years (brand-name product

only) and MDD in pediatric patients aged ≥12 years.

- Fluoxetine: Safety and effectiveness have been established for treating MDD in pediatric patients aged ≥8 years and OCD in pediatric patients aged ≥7 years.
- Fluvoxamine immediate-release: Safety and effectiveness have been established for the treatment of OCD in pediatric patients aged ≥8 years.
- Sertraline: Safety and effectiveness have been established for the treatment of OCD in pediatric patients aged ≥6 years.

Pregnancy

- Observational studies indicate that exposure to SSRIs, particularly in the month before delivery, is associated with a <2-fold increased risk of postpartum hemorrhage. Exposure to SSRIs may also increase the risk of persistent pulmonary hypertension of the newborn and poor neonatal adaptation.
- Citalopram: Epidemiologic studies have not identified developmental risks associated with use during pregnancy.
- Escitalopram: Epidemiologic studies have not identified developmental risks associated with use during pregnancy.
- Fluoxetine: Epidemiologic studies have not identified developmental risks associated with use during pregnancy.
- Fluvoxamine: Observational studies have not identified developmental risks associated with use during pregnancy.
- Paroxetine: Epidemiologic studies indicate first-trimester exposure increases risk of congenital malformations.
- Sertraline: Epidemiologic studies have not identified developmental risks associated with use during pregnancy.

Renal Disease

- No renal dosage adjustments are recommended in the labeling for citalopram, escitalopram, fluoxetine, fluvoxamine, or sertraline.
- Paroxetine: Reduce initial dosage in patients with severe renal impairment.

Hepatic Disease

- Citalopram: Maximum recommended daily dose in patients with hepatic impairment is 20 mg.
- Escitalopram: Maximum recommended daily dose in patients with hepatic impairment is 10 mg.
- Fluoxetine: Lower or less frequent doses should be used in patients with cirrhosis.

- Fluvoxamine: Consider dosage adjustment in patients with hepatic impairment.
- Paroxetine: Reduce initial dosage in patients with severe hepatic impairment.
- Sertraline: Reduce dosage in patients with mild hepatic impairment (Child-Pugh score 5 or 6). Use is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh >6).

Current Clinical Guideline Recommendations[8-19]

Bulimia Nervosa

- **American Psychiatric Association: 2023**
  - For adults with bulimia nervosa, eating disorder-focused cognitive behavioral therapy (CBT) is recommended. A serotonin reuptake inhibitor (e.g., fluoxetine) is also recommended, either as part of initial treatment or for patients with minimal or no response to CBT after 6 weeks.

Generalized Anxiety Disorder

- **American College of Obstetricians and Gynecology (ACOG): 2023**
  - In patients with perinatal depression or anxiety disorders or with PTSD, the use of an antidepressant that has worked before is preferred. For antidepressant-naïve patients, SSRIs (particularly sertraline, fluoxetine, citalopram, or escitalopram) are preferred in the first-line setting. SNRIs are reasonable alternatives.
- **World Federation of Societies of Biological Psychiatry (WFSBP): 2023**
  - First-line pharmacologic therapies for GAD include SSRIs (escitalopram, paroxetine, and sertraline) and SNRIs (duloxetine and venlafaxine).
- **American Academy of Child and Adolescent Psychiatry: 2020**
  - SSRIs should be offered to patients aged 6 to 18 years with GAD.
  - SNRIs could be offered to patients aged 6 to 18 years with GAD.

Major Depressive Disorder

- **ACOG: 2023**

- In patients with perinatal depression or anxiety disorders or with PTSD, the use of an antidepressant that has worked before is preferred. For antidepressant-naïve patients, SSRIs (particularly sertraline, fluoxetine, citalopram, or escitalopram) are preferred in the first-line setting. SNRIs are reasonable alternatives.

- **American College of Physicians: 2023**
  - First-line pharmacologic therapies for adults with acute-phase moderate to severe MDD include SSRIs and SNRIs.
- **Veterans Affairs/Department of Defense (VA/DoD): 2022**
  - First-line pharmacologic therapies for uncomplicated mild to moderate MDD include SSRIs, SNRIs, mirtazapine, bupropion, trazodone, vilazodone, or vortioxetine.
- **American Academy of Pediatrics: 2018**
  - For adolescents with MDD who are managed in a primary care setting, initial recommended therapies include psychotherapy and/or antidepressant therapy, such as SSRIs.

Obsessive Compulsive Disorder

- **WFSBP: 2023**
  - SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) are first-line pharmacologic therapy for patients with OCD. Clomipramine is also effective, but it is unclear whether it is more effective than SSRIs.
  - Treatment with CBT/exposure and response prevention (ERP) in combination with pharmacologic treatment is more effective than pharmacologic treatment alone. However, combined treatment with CBT/ERP and pharmacologic treatment is not more effective than CBT/ERP alone.

Panic Disorder

- **ACOG: 2023**
  - In patients with perinatal depression or anxiety disorders or with PTSD, the use of an antidepressant that has worked before is preferred. For antidepressant-naïve patients, SSRIs (particularly sertraline, fluoxetine, citalopram, or escitalopram) are preferred in the first-line setting. SNRIs are reasonable alternatives.
- **WFSBP: 2023**

- First-line pharmacologic therapies for panic disorder include SSRIs and venlafaxine. Clomipramine and imipramine may also be considered but are less preferred due to tolerability.

Premenstrual Dysphoric Disorder

- **International Society for Premenstrual Disorders: 2016**
  - SSRIs should be considered among first-line treatments for patients with premenstrual dysphoric disorder (PMDD).

Posttraumatic Stress Disorder

- **ACOG: 2023**
  - In patients with perinatal depression or anxiety disorders or with posttraumatic stress disorder (PTSD), the use of an antidepressant that has worked before is preferred. For antidepressant-naïve patients, SSRIs (particularly sertraline, fluoxetine, citalopram, or escitalopram) are preferred in the first-line setting. SNRIs are reasonable alternatives.
- **VA/DoD: 2023**
  - Psychotherapy is recommended over pharmacologic therapy for the treatment of PTSD.
  - Paroxetine, sertraline, or venlafaxine are recommended for pharmacologic treatment of PTSD.
- **WFSBP: 2023**
  - Fluoxetine, paroxetine, sertraline, and venlafaxine are first-line pharmacologic therapies for PTSD. Amitriptyline is also effective but is associated with more side effects than the SSRI/SNRI treatment options.

Social Anxiety Disorder

- **ACOG: 2023**
  - In patients with perinatal depression or anxiety disorders or with PTSD, use of an antidepressant that has worked before is preferred. For antidepressant-naïve patients, SSRIs (particularly sertraline, fluoxetine, citalopram, or escitalopram) are preferred in the first-line setting. SNRIs are reasonable alternatives.
- **WFSBP: 2023**
  - First-line pharmacologic therapies for social anxiety disorder include SSRIs and venlafaxine.

Vasomotor Symptoms of Menopause

- **North American Menopause Society: 2023**
  - Hormone therapy is the first-line treatment for vasomotor symptoms of menopause (VMS) in healthy women but may not be appropriate in all cases.
  - CBT, clinical hypnosis, SSRIs, SNRIs, gabapentin, and fezolinetant are recommended for the treatment of VMS based on good/consistent scientific evidence; weight loss and stellate ganglion block are also recommended based on limited/inconsistent scientific evidence and/or consensus/expert opinion.
- **Endocrine Society: 2015**
  - Hormone therapy is suggested for menopausal women aged <60 years or <10 years past menopause with bothersome VMS without contraindications or excess risk of cardiovascular disease or breast cancer.
  - For patients with moderate to severe VMS for whom pharmacologic therapy is indicated and hormone therapy is contraindicated or not preferred, SSRIs, SNRIs, gabapentin, or pregabalin are recommended.

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