VA
U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Service

A QUICK REFERENCE GUIDE (2020)

Depression

Clinical Pearls for Depression Management

VA PBM Academic Detailing Service

Real Provider Resources

Real Patient Results

Your Partner in Enhancing Veteran Health Outcomes

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DSM-5 Criteria for Major Depressive Disorder [1]

Five or more of the following symptoms have been present and documented during the same two-week period and represent a change from previous functioning: at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure.

Depressed mood OR Loss of interest or pleasure

Insomnia or hypersomnia

Psychomotor agitation or retardation

Fatigue or loss of energy

Change in appetite or significant weight gain or loss

Feelings of worthlessness or excessive guilt

Difficulty concentrating or indecisiveness

Thoughts of death or suicidality

Symptoms must be present nearly every day, with the exception of weight change and suicidal ideation.

Comparison Among Commonly Used Antidepressants [2–5*]

Drug	Safety						Notes
	Anti-Ach	Sedation	GI	Withdrawal	Drug Interactions	OD Risk[1,2]	
Citalopram	+	+	N ++	++	++	++	Higher doses may cause QT prolongation.
Escitalopram	+	+	N ++	++	+	++	Supratherapeutic (30 mg/day) doses are associated with QT prolongation. Use with caution in patients with multiple risk factors for QT prolongation.
Fluoxetine	+	+	N ++	+	+++	+	No need to taper with discontinuation; good for poor adherence.
Paroxetine	++	++	N,D ++	+++	+++	+	High risk of discontinuation syndrome
Sertraline	+	+	N,D ++	++	++	+	Medication of choice for pregnancy and breastfeeding

*Data taken from package inserts. Anti-ach = anticholinergic; BP = blood pressure; C = constipation, CrCL = creatinine clearance; D = diarrhea; ESRD = end stage renal disease; GI = gastrointestinal; OD = overdose; N = nausea/vomiting; NE = norepinephrine.
+ = less common; ++ = intermediate; +++ = more common.

continued from page 2 (Comparison Among Commonly Used Antidepressants [2–5])*

Drug	Safety						Notes
	Anti-Ach	Sedation	GI	Withdrawal	Drug Interactions	OD Risk[1,2]	
Duloxetine	+	+	N ++	+++	++	++	Not recommended for use in patients with hepatic impairment, CrCl <30 ml/min, or ESRD. High risk of discontinuation syndrome. May increase BP.
Venlafaxine	+	+	N ++	+++	++	++	May increase BP at high doses; doses >150 mg when NE reuptake maximized; high risk discontinuation syndrome.

*Data taken from package inserts. Anti-ach = anticholinergic; BP = blood pressure; C = constipation, CrCL = creatinine clearance; D = diarrhea; ESRD = end stage renal disease; GI = gastrointestinal; OD = overdose; N = nausea/vomiting; NE = norepinephrine.
+ = less common; ++ = intermediate; +++ = more common.

continued from page 2 (Comparison Among Commonly Used Antidepressants [2–5])*

Drug	Safety						Notes
	Anti-Ach	Sedation	GI	Withdrawal	Drug Interactions	OD Risk[1,2]	
Amitriptyline	+++	+++	C	++	++	+++	Dosed at bedtime; may cause postural hypotension; weight gain. Overdose can cause seizures and cardiac arrhythmia; can result in death. Blood levels useful in guiding therapy. Desipramine and nortriptyline are more tolerable, less sedating, less anticholinergic and cause less orthostatic hypotension.
Desipramine	++	++	C	++	++	+++	
Imipramine	+++	+++	C	++	++	+++	
Nortriptyline	++	++	C	++	++	+++	

*Data taken from package inserts. Anti-ach = anticholinergic; BP = blood pressure; C = constipation, CrCL = creatinine clearance; D = diarrhea; ESRD = end stage renal disease; GI = gastrointestinal; OD = overdose; N = nausea/vomiting; NE = norepinephrine.
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Drug	Safety						Notes
	Anti-Ach	Sedation	GI	Withdrawal	Drug Interactions	OD Risk[1,2]	
Bupropion	+	+	+	+	++	++	Avoid if history of seizure or eating disorder. Minimal sexual side effects; may assist with smoking cessation. Abrupt discontinuation of alcohol or benzodiazepines can increase seizure risk.
Mirtazapine	++	+++	+	++	++	+	Can increase appetite and cause weight gain; minimal sexual side effects. Sedating, so may help with sleep problems (doses >15 mg may be less sedating).

*Data taken from package inserts. Anti-ach = anticholinergic; BP = blood pressure; C = constipation, CrCL = creatinine clearance; D = diarrhea; ESRD = end stage renal disease; GI = gastrointestinal; OD = overdose; N = nausea/vomiting; NE = norepinephrine.
+ = less common; ++ = intermediate; +++ = more common.

Antidepressant Dosing [2,6]

	Agent	Initial Dose (mg)	Titration Schedule (mg)	Maximum Dose/Day (mg)	Guidance in Special Populations		
					Geriatric (starting dose, mg)	Renal	Hepatic
SSRIs	Citalopram*	20 daily	20 weekly	40; 20 geriatric	10 daily	Avoid: CrCl <20 ml/min	Reduced hepatic function: max 20 mg/day
SSRIs	Escitalopram	10 daily	10 weekly	20	5 daily	Avoid: CrCl <20 ml/min	Reduced hepatic function: max 10 mg/day
SSRIs	Fluoxetine	20 daily	20 every 2 weeks	80	10 daily	No change	With cirrhosis (no ascites): ↓ dose 50%
SSRIs	Paroxetine	20 daily	10–20 weekly	50	10 daily	Max 40 mg CrCl <30 ml/min	Severe: max dose 40 mg/day

*If >60 years old, hepatic impairment, poor CYP2C19 metabolizer, or on cimetidine the maximum dose is 20mg daily; Hepatic impairment using Child-Pugh, mild class A (5–6), moderate class B (7–9), severe class C (10–15). 5-HT3 = serotonin; Antag = receptor antagonist; CrCl = creatinine clearance; DNRI = Dopamine-Norepinephrine Reuptake Inhibitor; N/A = not applicable; NaSSA = Noradrenergic and Specific Serotonergic Antidepressant; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant.

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	Agent	Initial Dose (mg)	Titration Schedule (mg)	Maximum Dose/Day (mg)	Guidance in Special Populations		
					Geriatric (starting dose, mg)	Renal	Hepatic
SSRIs	Sertraline	50 daily	50 weekly	200	25 daily	No change	Mild: ↓ dose 50%
SSRIs	Vilazodone	10 daily	10 weekly	20–40	5 daily	No change	No change
SNRIs	Duloxetine	30 daily	30 weekly	120; no benefit at doses >60 mg daily	20 daily	Avoid: CrCl <30 mL/min	Avoid with any impairment
SNRIs	Desvenlafaxine	50 daily	N/A	100; no benefit at doses >50 mg daily	25 daily	CrCl = 30–50, mL/min, 50 mg daily; CrCl <30 mL/min, 25 mg daily	No change

*If >60 years old, hepatic impairment, poor CYP2C19 metabolizer, or on cimetidine the maximum dose is 20mg daily; Hepatic impairment using Child-Pugh, mild class A (5–6), moderate class B (7–9), severe class C (10–15). 5-HT3 = serotonin; Antag = receptor antagonist; CrCl = creatinine clearance; DNRI = Dopamine-Norepinephrine Reuptake Inhibitor; N/A = not applicable; NaSSA = Noradrenergic and Specific Serotonergic Antidepressant; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant.

continued from page 6 (Antidepressant Dosing [2,6])

	Agent	Initial Dose (mg)	Titration Schedule (mg)	Maximum Dose/Day (mg)	Guidance in Special Populations		
					Geriatric (starting dose, mg)	Renal	Hepatic
SNRIs	Venlafaxine IR	37.5 mg twice daily	75 weekly	225–375	12.5 to 25 daily	CrCl= 10–70 mL/min, ↓ dose 25%	Mild to moderate: ↓ dose 50%
SNRIs	Venlafaxine XR	75 mg daily	75 weekly	225	37.5 to 75 daily	CrCl= 30–89 mL/min, ↓ dose 25 to 50%; CrCl < 30 mL/min, ↓ dose 50%	Mild to moderate: ↓ dose 50%
SNRIs	Levomilnacipran	20 daily	20–40 mg every 2 days	120	20 daily	CrCl= 30–59 mL/min, 80 mg max daily; CrCl= 15–29 mL/min, 40 mg max daily	No Change

*If >60 years old, hepatic impairment, poor CYP2C19 metabolizer, or on cimetidine the maximum dose is 20mg daily; Hepatic impairment using Child-Pugh, mild class A (5–6), moderate class B (7–9), severe class C (10–15). 5-HT3 = serotonin; Antag = receptor antagonist; CrCl = creatinine clearance; DNRI = Dopamine-Norepinephrine Reuptake Inhibitor; N/A = not applicable; NaSSA = Noradrenergic and Specific Serotonergic Antidepressant; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant.

continued from page 6 (Antidepressant Dosing [2,6])

	Agent	Initial Dose (mg)	Titration Schedule (mg)	Maximum Dose/Day (mg)	Guidance in Special Populations		
					Geriatric (starting dose, mg)	Renal	Hepatic
DNRIs	Bupropion IR	100 twice daily	100 weekly	450 (3 divided doses)	37.5 to 75 twice daily	↓ dose	Severe: max dose 75 mg daily
DNRIs	Bupropion SR	150 daily	150 weekly	450 (2 divided doses)	100 daily	↓ dose	Severe: max dose 100 mg daily or 150 every other day; Extreme caution
DNRIs	Bupropion XR	150 daily	150 weekly	450	150 daily	↓ dose	Severe: max dose 150 mg every other day; Extreme caution

*If >60 years old, hepatic impairment, poor CYP2C19 metabolizer, or on cimetidine the maximum dose is 20mg daily; Hepatic impairment using Child-Pugh, mild class A (5–6), moderate class B (7–9), severe class C (10–15). 5-HT3 = serotonin; Antag = receptor antagonist; CrCl = creatinine clearance; DNRI = Dopamine-Norepinephrine Reuptake Inhibitor; N/A = not applicable; NaSSA = Noradrenergic and Specific Serotonergic Antidepressant; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant.

continued from page 6 (Antidepressant Dosing [2,6])

	Agent	Initial Dose (mg)	Titration Schedule (mg)	Maximum Dose/Day (mg)	Guidance in Special Populations		
					Geriatric (starting dose, mg)	Renal	Hepatic
NaSSa	Mirtazapine	15 at bedtime	15 weekly	45	7.5 at bedtime	CrCl <40 ml/min use caution	Titrate slowly
5-HT3 antag	Vortioxetine	10 daily	10 daily	5–20	5–10 daily	No change	Mild to moderate: no change; Severe: not recommended
TCA	Amitriptyline	25–50 at bedtime or divided doses	Weekly	300	10 to 25 daily	No change	Lower dose and slower titration recommended

*If >60 years old, hepatic impairment, poor CYP2C19 metabolizer, or on cimetidine the maximum dose is 20mg daily; Hepatic impairment using Child-Pugh, mild class A (5–6), moderate class B (7–9), severe class C (10–15). 5-HT3 = serotonin; Antag = receptor antagonist; CrCl = creatinine clearance; DNRI = Dopamine-Norepinephrine Reuptake Inhibitor; N/A = not applicable; NaSSA = Noradrenergic and Specific Serotonergic Antidepressant; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant.

continued from page 6 (Antidepressant Dosing [2,6])

	Agent	Initial Dose (mg)	Titration Schedule (mg)	Maximum Dose/Day (mg)	Guidance in Special Populations		
					Geriatric (starting dose, mg)	Renal	Hepatic
TCA	Imipramine	25–50 at bedtime or divided doses	Weekly	300	10 to 25 daily	No change	Lower dose and slower titration recommended
TCA	Nortriptyline	25 daily or at bedtime	Weekly	150	10 to 25 daily	No change	Lower dose and slower titration recommended
TCA	Desipramine	25–50 at bedtime or divided doses	Weekly	300; 150 geriatric	10 to 25 daily	No change	Lower dose and slower titration recommended

*If >60 years old, hepatic impairment, poor CYP2C19 metabolizer, or on cimetidine the maximum dose is 20mg daily; Hepatic impairment using Child-Pugh, mild class A (5–6), moderate class B (7–9), severe class C (10–15). 5-HT3 = serotonin; Antag = receptor antagonist; CrCl = creatinine clearance; DNRI = Dopamine-Norepinephrine Reuptake Inhibitor; N/A = not applicable; NaSSA = Noradrenergic and Specific Serotonergic Antidepressant; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant.

PHQ-9: Depression Severity and Treatment Response[7]

Depression Severity			
Minimal PHQ-9 = 0–9	Mild PHQ-9 = 10–14	Moderate PHQ-9 = 15–19	Severe PHQ-9 ≥20

Use an effective antidepressant dose for at least six to eight weeks.[8] A ≥25% reduction in baseline PHQ-9 score by week six indicates a patient may benefit from an increase in dose (if tolerated) or further exposure for as many as 12–14 weeks.[3,8]

Monitoring Treatment Response		
Remission: PHQ-9 score ≤4 for at least one month	Partial response: • Five-point score reduction or • A score >4 and <10 on PHQ-9 or • >25% decrease from baseline	Non-response: • Less than five-point score reduction or • ≤25% decrease from baseline
Continue Current Regimen	***Continue or increase current dosage***	***Maximize dosage or switch***

Switching Antidepressants [9–11]

Initial Medication	SSRIs, and Vortioxetine	SNRIs	Mirtazapine	Bupropion	TCAs	MAOIs‡	Equivalent Doses (mg)+
Citalopram	+	+	++	++	++	+++	20
Escitalopram	+	+	++	++	++	+++	10
Fluoxetine*	+	+	+	+	+++	+++	20
Paroxetine*	+	+	++	++	++	+++	20
Sertraline	+	+	++	++	++	+++	50
Vilazodone	+	+	++	++	++	+++	10
Vortioxetine	+	+	++	++	++	+++	10

Cross-taper generally takes one to two weeks. *May increase serum concentration of TCAs, SNRIs, bupropion and vortioxetine; therefore, start at low dose to avoid toxicity. +Equivalent doses are approximate and may vary based on patient-specific factors such as sensitivity to medication side effects and concomitant medications. ‡MAOIs – Wait two weeks after discontinuation of an MAOI before starting another antidepressant; wait two weeks after discontinuing an antidepressant before starting an MAOI, except fluoxetine which needs a washout period of at least five weeks. MAOI = Monoamine Oxidase Inhibitor; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant. + = direct switch probably safe; ++ = cross-taper recommended; +++ = washout period advisable.

continued from page 13 (Switching Antidepressants [9–11])

Initial Medication	SSRIs, and Vortioxetine	SNRIs	Mirtazapine	Bupropion	TCAs	MAOIs‡	Equivalent Doses (mg)+
Duloxetine*	+	+	++	++	++	+++	30
Venlafaxine	+	+	++	++	++	+++	75
Desvenlafaxine	+	+	++	++	++	+++	50
Levomilnacipran	+	+	++	++	++	+++	20
Mirtazapine	++	++		++	++	+++	15
Bupropion XR*	+	++	++		++	+++	150
TCAs	++	++	++	++		+++	
MAOIs‡	+++	+++	+++	+++	+++	+++	

Cross-taper generally takes one to two weeks. *May increase serum concentration of TCAs, SNRIs, bupropion and vortioxetine; therefore, start at low dose to avoid toxicity. +Equivalent doses are approximate and may vary based on patient-specific factors such as sensitivity to medication side effects and concomitant medications. ‡MAOIs – Wait two weeks after discontinuation of an MAOI before starting another antidepressant; wait two weeks after discontinuing an antidepressant before starting an MAOI, except fluoxetine which needs a washout period of at least five weeks. MAOI = Monoamine Oxidase Inhibitor; SNRI = Serotonin Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant. + = direct switch probably safe; ++ = cross-taper recommended; +++ = washout period advisable.

Identifying Discontinuation Symptoms by System [12]

System	Symptoms
General	Chills, malaise, flu-like symptoms, fatigue, lethargy, fever, diaphoresis, dizziness
Eyes, Ears, Nose, Mouth, Throat	Blurred vision, eye movement abnormalities, sore eyes, eye twitch, tinnitus, rhinorrhea, sinus congestion, nasal congestion, increased salivation
Respiratory	Shortness of breath
Cardiovascular	Palpitation, tachycardia, elevated blood pressure
Gastrointestinal, Genitourinary	Nausea, vomiting, diarrhea, abdominal pain, stomach cramps, abdominal bloating, genital hypersensitivity, premature ejaculation
Musculoskeletal	Sore muscles, myalgia, arthralgia, muscle cramps
Skin And Hair	Pruritus
Neurological	Disequilibrium, sensory disturbances (unusual sensitivity to sound, electric shock–like sensations, paresthesia, dysgeusia, and brain zaps), neuromuscular symptoms (acute dystonia, myoclonus, tremor, shaking, akathisia), cognitive symptoms (delirium, amnesia, memory impairments, disorientation, confusion)
Psychiatric	Worsening of mood, exacerbation of anxiety, sleep disruption, perceptual impairments (depersonalization, hypnagogic hallucination, auditory and visual hallucinations)

Reducing Antidepressant Discontinuation Syndrome [9,12,13]

Educate patients on the risk of discontinuation syndrome with antidepressant use.

Half-life	Taper Duration	Additional Recommendations
≥24 hours (e.g., escitalopram, fluoxetine*, mirtazapine, sertraline)	2 to 4 weeks	• Mild symptoms that occur despite a gradual taper can be managed with reassurance and watchful waiting. • Moderate to severe symptoms that occur during taper: - Decrease pace of taper. • Moderate to severe symptoms that occur after discontinuation: - Restart at the dose at which there were no symptoms and decrease pace. • Switching to fluoxetine (10 to 20 mg) may be a reasonable option for those who cannot tolerate a slow taper.
<24 hours (e.g., duloxetine, paroxetine, venlafaxine)	2 to 3 months	

*Fluoxetine and bupropion not generally associated with discontinuation syndrome. Vortioxetine 10 mg no taper needed; higher doses taper over a week. Monoamine Oxidase Inhibitors need to be tapered over one to six months depending on duration of use.

Antidepressants and Sexual Dysfunction[15–20]

Baseline sexual dysfunction should be assessed. Worsening could be secondary to medications and can lead to decreased medication adherence. It may also indicate progression of disease state and requires evaluation.

Sample question: *Have you noticed any problems in your sexual desire, your orgasms/ejaculation, or your arousal capacity since you started taking the medication?*[14]

Sexual Dysfunction Treatment Strategies [9,14,21–23]

Initial Treatment

- Wait – Within six months, ~10% of patients report remission of sexual dysfunction, and 15–20% report symptom improvement.
- Decrease dose – Higher doses have been associated with higher rates of dysfunction; may lead to reduced antidepressant effect.

If sexual dysfunction continues, management should be determined by the severity of depression and sexual dysfunction.

Sexual Dysfunction Treatment Strategies[9,14,21–23]		
Antidepressant Response	**Partial or no response** (<50% improvement from baseline PHQ-9)	**Moderate response or remission** (≥50% improvement from baseline PHQ-9)
Treatment Options	**Switch Antidepressants**: Bupropion, mirtazapine, vortioxetine, nefazodone are associated with a lower incidence of sexual dysfunction. *Consider EBP as an alternate treatment*.	**Severe sexual dysfunction** (impairment occurs almost always during sexual activity) • Consider switching antidepressants or utilizing EBP as an alternate treatment.
		Mild to moderate sexual dysfunction (impairment occurs half the time during sexual activity): Augment antidepressant with another drug. • Males: - Phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, tadalafil) improve antidepressant-induced erectile dysfunction. • Females: - Bupropion (300 mg day) may be effective as adjunctive therapy for low libido. - Phosphodiesterase-5 inhibitors for delayed orgasm or anorgasmia

EBP = evidence-based psychotherapy

Antidepressants and Hyponatremia

- All antidepressants have been associated with cases of hyponatremia.[9,24,25]
- Onset can occur from three days to the first few weeks after starting medication.[9,26]
- Not thought to be dose related[9]
- Monitor for hyponatremia especially in higher risk patients.[9]
  - Serum electrolyte panel and symptoms (dizziness, nausea, lethargy, confusion, cramps, seizures)

Risk Factors of Hyponatremia[9,25,27]

Demographic	Co-medications		Medical Comorbidities		
Old age*	Antipsychotics	Omeprazole	Diabetes	Glomerular filtration rate <50 mL/min	Recent history of pneumonia
Female	Carbamazepine	Oxcarbazepine	Hypothyroidism	Low baseline sodium	History of hyponatremia
Living in warm weather climate	Chemotherapy	Thiazide Diuretics	COPD	Various cancers	Hypertension and/ or heart failure
	NSAIDs and Tramadol	Trimethoprim	Low body weight	Head injury or CVA	

*Hyponatremia is common in elderly patients, making monitoring essential. COPD = Chronic Obstructive Pulmonary Disease; CVA = Cerebrovascular Accident.

After discontinuation of the offending antidepressant, hyponatremia typically resolves within two weeks.[28]

Restarting an Antidepressant after Hyponatremia has Resolved
Select an agent from a different class – There have been fewer case reports of recurrence of hyponatremia when an agent with a different mechanism of action is selected (e.g., mirtazapine, bupropion, nortriptyline).[9,25,29]
Consider withdrawing other medications associated with hyponatremia (e.g., thiazide diuretics, carbamazepine, NSAIDs, tramadol, proton pump inhibitors).[9,27]
Start low, go slow, and monitor serum sodium closely.[9]
Consider long-term maintenance strategies if drug therapy with offending agent is necessary (e.g., fluid restriction, careful use of oral demeclocycline*).[9,27]

Serotonin Reuptake Inhibitors and GI Bleeding

Serotonin reuptake inhibitors (e.g., SSRI, SNRI) have been associated with increased risk of GI bleed (odds ratio of 1.5 to 1.6).[9,30,31] This risk increases fourfold with concurrent treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), and two to threefold with concurrent aspirin; the risk is lowered by acid-suppressing drugs.[9,30,31]

Risk Factors for Bleeding with Serotonin Reuptake Inhibitors[9,32]	
History of GI bleed	Active peptic ulcer disease
Elderly	Liver disease
Drugs that ↑ risk of bleeding (e.g., warfarin, aspirin)	Surgical procedures
Drugs that cause GI injury (e.g., NSAIDs)	

Management Strategies[9,32,33]
Consider switching to a non–serotonin reuptake inhibitor antidepressant, if appropriate. • Risk of bleeding present for as long as the serotonin reuptake inhibitor is present. • Mirtazapine, bupropion, and/or MAOI recommended in patients at risk for bleeding. • Nortriptyline and protriptyline may also be safe alternatives.
Consider addition of acid–suppressing agents (PPI or H2 blocker) in patients at risk for GI bleed (e.g., NSAID + SSRI).[9,34]

H2 = Histamine 2; MAOI = Monoamine Oxidase Inhibitor; PPI = Proton-pump Inhibitor; SNRI = Serotonin Norepinephrine Reuptake Inhibitors; SSRI = Selective Serotonin Reuptake Inhibitor.

Serotonin Syndrome [9,35–37]

Most patients present with serotonin syndrome within six to 24 hours after initial use of medication or change in dose.

Signs and Symptoms of Serotonin Syndrome	
Neurologic	Confusion, agitation, ataxia, akathisia
Neuromuscular	Clonus, hyperreflexia, tremor
Autonomic	Sweating, nausea, diarrhea, ↑ heart rate, ↑ blood pressure, ↑ temperature

Medications Associated with Serotonin Syndrome [15,16]		
Most antidepressants	Linezolid	Metoclopramide
Lithium	Reserpine	Dextromethorphan
Valproate	Sibutramine	Ginseng
Triptans	Tramadol	St. John's Wort
Buspirone	Fentanyl	Tryptophan

Strategies for Prevention	Treatment After Serotonin Syndrome
• When augmenting, use non–serotonergic agents if possible (e.g., bupropion). • Patient education: - Signs and symptoms of serotonin syndrome - Over–the–counter agents (e.g., dextromethorphan, St. John's Wort) may ↑ risk of serotonin syndrome.	If a serotonergic medication is required, restart only after symptoms of serotonin syndrome are no longer present. Use low doses and titrate slowly.

Augmenting Agents in Treatment Resistant Depression (TRD) [6,9,38,39]

Buspirone			
Medication	**Target Dose (mg)**	**Common Side Effects**	**Monitoring**
Buspirone	15–20 daily in 2 divided doses; max dose = 60 daily	Dizziness, nausea, headache, nervousness	Not recommended in patients with severe hepatic dysfunction.

Lithium and Triiodothyronine (T3)						
Medication	**Initial Dose**	**Renal Adjustment**	**Target Dose**	**Target Level**	**Side Effects**	**Monitoring**
Lithium*	300 mg daily	CrCL 30 to 89 mL/min: decrease dose CrCL <30 mL/min: avoid use	600–1,200 mg/day	0.4–1 mEq/L	GI upset, tremor, polyuria, polydipsia, weight gain, hypothyroidism, leukocytosis	EKG, CBC, TFTs, BMP, lithium level
Triiodothyronine (T3)**	25 mcg daily		50 mcg daily	N/A	Hyperthyroidism (anxiety, tremor, palpitations, insomnia, ↑ risk of osteoporosis and/or atrial arrhythmias)	TFTs

*Reduces the risk of suicide; **Due to ease of use and tolerability, triiodothyronine (T3) may be a more favorable option.
EKG = Electrocardiogram; CBC = Complete Blood Count; TFT = Thyroid Function Tests; BMP = Basic Metabolic Panel.

Clinical Pearls — Lithium[40]	
ACE–Is, ARBs, thiazide diuretics, NSAIDs interactions	Can ↑ lithium level up to 4 times; monitor lithium levels and adjust as needed.
Pregnancy Category D	Avoid in first trimester due to risk of Ebstein's anomaly for planned pregnancies.
Chronic therapy can result in nephrogenic diabetes insipidus.	Usually reversible when lithium is discontinued.
Adequate hydration needed to prevent fluctuations in lithium level.	Recommend patients drink 2–3 L water/day.

ACE-I = Angiotensin-Converting-Enzyme Inhibitor; ARB = Angiotensin II Receptor Blockers; NSAID = Nonsteroidal Anti-Inflammatory Drugs.

Augmenting Agents in Treatment Resistant Depression (TRD)[9,41] *(cont.)*

Antipsychotics			
Medication	**Target Dose (mg)**	**Common Side Effects**	**Monitoring**
Aripiprazole	5–20 daily	Akathisia, restlessness	• Assess for initial and continued response. • Cardiometabolic monitoring - Weight - Blood Pressure* - HgA1c or fasting plasma glucose* - Fasting lipids* • Monitor for movement disorders - Tardive dyskinesia - Extrapyramidal side effects • Screen for symptoms of hyperprolactinemia • Pregnancy test, if applicable. *Monitor at baseline, 12 weeks, then annually.
Brexpiprazole	1–3 daily	Akathisia, weight gain	
Cariprazine	2–4.5 daily	Akathisia, insomnia, nausea	
Olanzapine	5–20 daily	High risk weight gain, cardiometabolic changes	
Olanzapine + fluoxetine	6–18 daily + 25–50 daily	High risk weight gain, cardiometabolic changes	
Quetiapine	150–300 daily	Sedation, dry mouth, cardiometabolic changes, orthostatic hypotension	
Risperidone	0.25–4 daily	Sedation, dry mouth, hypotension, hyperprolactinemia	
Ziprasidone	40–80 twice daily	Somnolence/fatigue, muscle twitching, irritability, agitation	

Monotherapy Agents in Treatment Resistant Depression: Monoamine Oxidase Inhibitors (MAO-Is) [2,6]

	Initial Dose (mg/day)	Dose Titration Increments (mg)	Dosage Range (mg/day)
Non-selective MAO Inhibitors			
Phenelzine (Nardil®)	15 three times daily	15 per week	Initial dose: 60–90* Maintenance: 15
Tranylcypromine (Parnate®)	10–30 twice daily	10 every 1–3 weeks	30–60
Isocarboxazid (Marplan)	20 BID–QID two to four times daily	10 every 2–4 days	40–60
MAO-B Selective Inhibitors			
Selegiline patch+	6 every 24 hours	3 every 2 weeks	6–12

*Maintain doses at 60 to 90 mg daily until maximum benefit is obtained, then slowly reduce dose over several weeks. MAOIs require a low tyramine diet, except the selegiline 6 mg/day patch. +Increase above 6 mg may not be necessary.

MAOIs and Tyramine

Because MAO inhibition also occurs in the gut, ingestion of tyramine can cause a life–threatening hypertensive crisis. Patients experiencing MAOI toxicity symptoms should seek immediate medical attention.

Selected Foods with High Tyramine Content[9,40]		
Tap beers, red wine	Smoked meat or fish	Soybeans
Aged cheese	Sauerkraut	Dried meats (e.g., salami)

Selected MAO–I Mental Health Medications Interactions[9,40]	
Amphetamines	↑ risk of hypertensive episode
Atomoxetine	↑ risk of hypertensive episode
Bupropion	↑ risk of neurotoxic effects
Serotonergic Medications	↑ risk of serotonin syndrome
Methadone, Tramadol, Meperidine	↑ risk of serotonin syndrome

MAOI Toxicity Symptoms[42]	
Mild	Agitation, diaphoresis, tachycardia, and mild temperature elevation
Moderate	Altered mental status, tachypnea, vomiting, dysrhythmias, hyperthermia, and hypertension
Severe	Severe hyperthermia, seizures, central nervous system (CNS) depression, coma, cardiorespiratory depression, muscle rigidity and myoclonus

Stimulants Studied in Treatment Resistant Depression*

Medication	Clinical Pearls	Amount of Evidence	Effect on MDD
Modafinil[43,44]	May have a role in patients with depression and fatigue/sleepiness symptoms.	++++	Potentially effective
Methylphenidate[43,45]	Monotherapy not shown to be effective; may be more effective in combination with an antidepressant.	++	Mixed results
Dextroamphetamine[46]	Very small sample size	+	Potentially effective
Lisdexamfetamine[47]	Have not been shown to be effective for depression.	+++	Not effective
Atomoxetine[48]		+	Not effective

Candidates have symptoms of anergia, anhedonia, fatigue, and hypersomnia. Contraindicated with anxiety, insomnia, psychosis, and substance use disorder. *Seek cardiology consultation before prescribing stimulants in patients with comorbid cardiovascular disease. Stimulants utilized for treatment-resistant depression should be managed by a mental health specialist.

IV Ketamine and IN Esketamine Comparison

	IV Ketamine*	IN Esketamine*
FDA-Approved Indication	Induction and maintenance of general anesthesia	Treatment-resistant depression (in conjunction with an oral antidepressant); Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior**
Onset of Action	Rapid	Rapid
Comparator Drug	Midazolam	Only compared to placebo
When to Use	In patients who do not achieve remission from at least four adequate antidepressant trials	In patients who do not achieve remission from at least four adequate antidepressant trials
Administration	Twice weekly	Twice weekly for four weeks (induction)
Duration	Individualized	Individualized
Restrictions	Requires Ketamine Safety Form to be completed after every treatment session and submitted to VAMedSAFE online.	Requires Esketamine Safety Form to be completed after every treatment session and submitted to VAMedSAFE online.
Rems	No	Yes
Cost/Pt/Yr ($)	$	$$$$

*For additional information see the National Protocol Guidance for intravenous ketamine infusion and intranasal esketamine for TRD. Please see VA PBM criteria for use and National Protocol Guidance for more detailed information regarding patient selection and use. Ketamine infusion may provide acute symptom improvement of suicidal ideation within 24 hours of treatment.[49] **The effectiveness in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated and does not preclude the need for hospitalization if clinically warranted.

Treatment Considerations for Electroconvulsive Therapy (ECT) vs. Transcranial Magnetic Stimulation (rTMS) [2,50–54]

	Pros	Cons	Relative Contraindications	Discussion
ECT	Higher remission rates	• More side effects • Need for sedation/ anesthesia • Higher risk, more complex procedure	• Cardiovascular disease • Space-occupying intracranial lesion with evidence of elevated intracranial pressure • Recent cerebral hemorrhage or stroke • Bleeding or otherwise unstable vascular aneurysm • Severe pulmonary disease	Appropriate for acute and severe MDD including psychotic depression or catatonia; most effective acute treatment for depression
rTMS	Fewer side effects	• Lower remission rates • Longer time to response • Minimal risks and side effects • Daily administration	• Epilepsy or history of seizures • Active substance use disorder • Tumor or other neuroanatomical abnormality near treatment site • Cochlear implants • Deep brain stimulators • Pacemakers/implantable medical devices • Presence of any ferromagnetic material in the head • Medications that decrease seizure threshold*	Appropriate for patients with severe, persistent, or recurrent MDD who are treatment resistant to and/ or intolerant of pharmacotherapy

*Should a clinician decide to treat individuals who are on one of these medications, it is recommended that careful monitoring and regular re-determination of the motor threshold be considered. ECT may reduce the risk of suicide in various patient populations.

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