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Re-evaluating the Use of Benzodiazepines

A Quick Reference Guide

VA Academic Detailing Service

Real Provider Resources
Real Patient Results

VA PBM Academic Detailing Service

Real Provider Resources

Real Patient Results

Your Partner in Enhancing Veteran Health Outcomes

VA PBM Academic Detailing Service Email Group:
PharmacyAcademicDetailingProgram@va.gov

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https://vaww.portal2.va.gov/sites/ad

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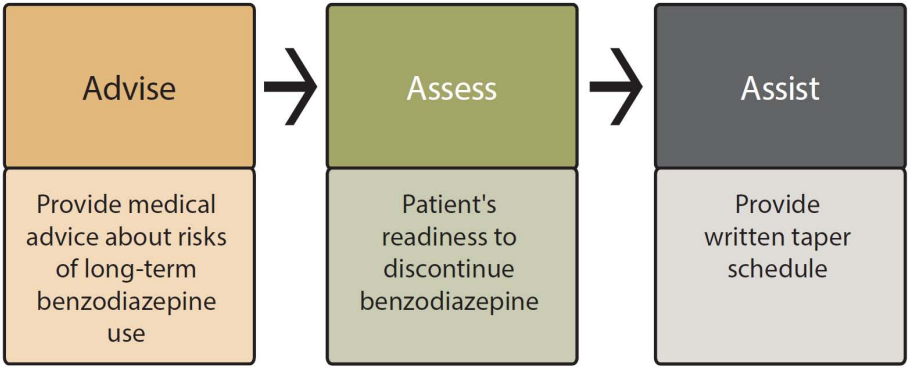
Discussing Benzodiazepine Withdrawal[1–6]

1. Assess patient's willingness to discontinue or reduce the dose of benzodiazepine

- Explore and acknowledge perceived benefits and harms and allow Veteran to express his/her concerns
- Explain the risks of continued use (disinhibition, ineffectiveness, loss of mental acuity) and the benefits of stopping
- If previous attempts have been made without success, explain that it is worth trying again



2. Agree on timing and discuss the symptoms likely to occur from withdrawal[5]

- Patients may experience withdrawal after >4 weeks of benzodiazepine use
- Timeline of withdrawal: occurs within 1–7 days and can last 4–14 days (short vs. long half-life, respectively)

Benzodiazepine Withdrawal Symptoms[5]	
Psychological	**Physical**
• Anxiety/irritability • Insomnia/nightmares • Depersonalization • Decreased memory and concentration • Delusion and hallucinations • Depression	• Stiffness • Weakness • Gastrointestinal disturbance • Flu like symptoms • Paresthesia • Visual disturbances • Seizures

3. Provide written instructions for a structured medication taper. Be prepared to slow the taper if the patient reports significant withdrawal symptoms

Benzodiazepine Equivalent Doses[1–3,5]						
	Chlordiazepoxide	Diazepam	Clonazepam	Lorazepam	Alprazolam	Temazepam
Approximate Dosage Equivalents	25 mg	10 mg	1 mg	2 mg	1 mg	15 mg
Elimination Half-life*	>100 hr	>100 hr	20–50 hr	10–20 hr	12–15 hr	10–20 hr

Benzodiazepine example dosage reduction and/or discontinuation:**

- Switching to a longer acting benzodiazepine may be considered if clinically appropriate[+]
- Reduce dose by 50% the first 4 weeks, maintain on that dose for 1–2 months, then reduce dose by 25% every 2 weeks

*Includes active metabolites; **these are suggestions only and a slower taper may be used (e.g. 10–25% every 4 weeks); [+]high dose alprazolam may not have complete cross tolerance, a gradual switch to clonazepam or diazepam before taper may be appropriate; in geriatric patients consider tapering the short acting agent until withdrawal symptoms are seen then switch to a longer acting agent; other treatment modalities (e.g. antidepressants for anxiety) should be considered if clinically appropriate.

Benzodiazepine Example Taper[1–3,5]	
Milestone Suggestions	**Example: Lorazepam 4 mg bid**
Week 2: Decrease dose by 25% Week 4: Decrease dose by 25% Weeks 5–8: Hold dose 1–2 months Week 9: Decrease dose by 25% every two weeks	Convert to 40 mg diazepam daily Week 1: 35 mg/day Week 2: 30 mg/ day (25% of initial dose) Week 3: 25 mg/day Week 4: 20 mg/day (50% of initial dose) Weeks 5–8: Continue at 20 mg/day for 1 month Weeks 9–10: 15 mg/day Weeks 11–12: 10 mg/day Weeks 13–14: 5 mg/day Week 15: Discontinue
These are suggestions only and a slower taper may be used (e.g. 10–25% every 4 weeks); in geriatric patients consider tapering the short acting agent until withdrawal symptoms are seen then switch to a longer acting agent; other treatment modalities (e.g. antidepressants for anxiety) should be considered if clinically appropriate.	

Potential Medication Augmentation Strategies for Benzodiazepine Withdrawal*		
Medication	**Evidence**	**Dosing Range**
Carbamazepine	• Case series and small open label studies indicate that carbamazepine may be helpful for BZD withdrawal symptoms[7,8] • Double blind placebo controlled study (n = 40; 4 week BZD taper) found trends towards carbamazepine superiority in reducing withdrawal symptoms; more pronounced if on >20 mg/day diazepam equivalents[9]	200–800 mg/day divided doses
Melatonin	• Double blind studies indicate that that CRM may improve subjective sleep quality but provide conflicting information on improving discontinuation rates[12,13] • Double blind studies have found no difference in withdrawal symptoms with the use of CRM compared to placebo[14, 15]	CRM 2 mg at bedtime

*Gradually tapering the benzodiazepine to minimized withdrawal symptoms is the preferred method of discontinuation or reduction of dose.
BZD = benzodiazepine; CRM = controlled release melatonin

Limited and conflicting evidence supports the use of adjuvant pharmacotherapy in decreasing the severity of benzodiazepine withdrawal.

continued

Potential Medication Augmentation Strategies for Benzodiazepine Withdrawal*		
Medication	**Evidence**	**Dosing Range**
Gabapentin	• 2 positive case reports of rapid inpatient BZD taper using gabapentin for withdrawal symptoms[10,11]	600–900 mg/day divided doses
Pregabalin	• Case reports and one observational non-comparative study indicate that pregabalin may reduce withdrawal symptoms[16,17]	150–450 mg/day (Mean = 300 mg/day)
Adding non-pharmacological interventions (e.g. CBT), self-help instructions, and patient education increases discontinuation outcomes.		
*Gradually tapering the benzodiazepine to minimized withdrawal symptoms is the preferred method of discontinuation or reduction of dose. BZD = benzodiazepine; CRM = controlled release melatonin		

Limited and conflicting evidence supports the use of adjuvant pharmacotherapy in decreasing the severity of benzodiazepine withdrawal.

Key Features of Specific Anxiety and Trauma Related Disorders[5,18]	
Disorder	**Key Features**
Generalized Anxiety Disorder	• Excessive irrational worries about multiple events or activities (e.g. school/work difficulties) • Physical symptoms like hyperventilation, tachycardia, sweating, muscle tension
Obsessive-Compulsive Disorder	• Obsessional recurrent thinking, urges, or images that cause marked anxiety or distress • Compulsive repetitive behavior (e.g. hand washing) or mental acts (e.g. counting) that individual feels driven to do to reduce anxiety evoked by obsessions
Panic Disorder	• Recurrent unexpected panic attacks (e.g. severe anxiety, accompanied by physical sensations such as shortness of breath, palpitations, or nausea), in the absence of obvious psychological causes or triggers • Persistent concern about additional panic attacks and/or maladaptive changes in behavior related to the attacks
Social Anxiety Disorder	• Extreme unrealistic fear of social situations (e.g. public speaking, eating in public) in which there is possible exposure to scrutiny by others • Avoidant behavior around feared situation
Posttraumatic Stress Disorder	• History of a traumatic life event (e.g. threatened death, serious injury, sexual violation), often occurring during combat, car accident, or violent crime • Intrusive symptoms (distressing memories, dreams, flashbacks); emotional numbness or detachment; avoidance of perceived similar situations; alterations in arousal and reactivity (e.g. irritable behavior, hypervigilance)

Management of Anxiety and Trauma Related Disorders[5,19,20]					
	Generalized Anxiety Disorder	Obsessive Compulsive Disorder	Panic Disorder	Social Anxiety Disorder	Posttraumatic Stress Disorder
Non-drug Treatments	CBT Exposure Therapy Applied Relaxation	Exposure Therapy CBT	CBT	CBT Exposure Therapy	CPT Prolonged Exposure EMDR
First-line Medication Treatment Options	SSRIs SNRIs Buspirone Mirtazapine Pregabalin	SSRIs Clomipramine	SSRIs Venlafaxine	SSRIs Venlafaxine	SSRIs Venlafaxine
Other Non-Benzodiazepine Medication Treatment Options (limited by evidence or side effects)	Hydroxyzine Quetiapine	Mirtazapine Venlafaxine Augmentation of SSRI: - Antipsychotics - Lamotrigine - Topiramate	Mirtazapine TCA	Gabapentin Pregabalin Propranolol*	Mirtazapine TCA Nefazodone Prazosin (nightmares)

CBT = cognitive behavioral therapy; CPT = cognitive processing therapy; EMDR = eye movement desensitization and reprocessing; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; *performance anxiety only. Benzodiazepines may be used for short-term emergency management of generalized anxiety and panic disorders and may be useful on an as needed basis for the management of social anxiety disorders.

Comparison Among Commonly Used Antidepressants for Anxiety and Trauma Related Disorders[5,21]							
Class	Drug	Anti–Chol	Sedation	GI	Withdrawal	Drug Interaction	Notes
SSRI	Citalopram*			N			May cause QT prolongation
	Escitalopram			N			
	Sertraline			N,D			
	Paroxetine			N			Dosed at bedtime; weight gain
	Fluoxetine			N			No need to taper with discontinuation
SNRI	Venlafaxine			N			May increase blood pressure at high doses
	Duloxetine			N			Monitor liver function
TCA	Amitriptyline			C			Dosed at bedtime; postural hypotension; weight gain; overdose can cause seizures, ventricular fibrillation tachycardia, and cardiac arrhythmia; urinary retention, especially in men with prostate enlargement
	Imipramine			C			
	Nortriptyline+			C			
	Desipramine+			C			
Other	Mirtazapine						Can increase appetite and cause weight gain
	Nefazodone			C,N			Rare but potentially serious hepatotoxicity; ↓ incidence of sexual dysfunction relative to SSRIs
	Phenelzine			C			Low tyramine diet required; dose related orthostasis

Anti-Chol = anticholinergic, GI = gastrointestinal, C = constipation, D = diarrhea, N = nausea/vomiting; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA= tricyclic antidepressant; *If >60 y/o, hepatic impairment, poor CYP 2C19 metabolizer OR on cimetidine, then max dose 20 mg; +These agents may have less anticholinergic, sedating, and hypotensive side effects than other TCAs; ***Higher antidepressant doses often needed in posttraumatic stress disorder and anxiety disorders, but be sure to start low and go slow – it's possible to worsen anxiety initially if dose is increased too quickly***

= less common
= intermediate
= more common

Common Pharmacologic Agents to Consider for Anxiety and Trauma Related Disorder[21,22]							
Class	Agent	Initial Dose	Maximum Dose/Day	Guidance in Special Populations			Additional Information
				Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment	
SSRI	Citalopram	10 mg DAILY	40 mg* DAILY	10–20 mg DAILY	Avoid: CrCl <20 ml/min	Max 20 mg/day	Tremor (8–16%), xerostomia (17–20%), somnolence (18%), headache (up to 18%), nausea (20–21%), vomiting (4–20%), ejaculation disorder (6.1%), QTc prolongation
	Escitalopram	10 mg DAILY	20 mg DAILY	5–20 mg DAILY	Avoid: CrCl <20 ml/min	Max 10 mg/day	Nausea (15 to 18%), vomiting (up to 3%), headache (up to 24%), ejaculation disorder (9–14%)
	Fluoxetine	10 mg DAILY	80 mg DAILY	5–40 mg DAILY	No adjustment; may accumulate norfluoxetine (neurotoxic)	↓ Dose 50%	Tremor (3–13%), insomnia (10–33%), headache (21%), nausea (12–29%), anxiety (6–15%)

*If >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine, max dose is 20 mg daily. BID = twice daily; CrCl = creatinine clearance; H1 = histamine; NaSSA = Noradrenergic and specific serotonergic antidepressant; PI = package insert; QHS = at bedtime; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TID = three times daily; $5HT_{1A}$ = serotonin

continued

Common Pharmacologic Agents to Consider for Anxiety and Trauma Related Disorder[21,22]							
Class	Agent	Initial Dose	Maximum Dose/Day	Guidance in Special Populations			Additional Information
				Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment	
SSRI	Paroxetine	10 mg QHS	50 mg QHS	10–40 mg DAILY	CrCl <30 ml/min: Max 40 mg	Max 40 mg/day	Tremor (4–11%), drowsiness (15–24%), nausea (19–26%), xerostomia (9–18%), ejaculatory disorder (13–28%)
	Sertraline	25 mg DAILY	200 mg DAILY	25–150 mg DAILY	No adjustment	↓ Dose 50%	Tremor (>10% in some cases), diarrhea (13–24%), nausea (13–30%), insomnia (12–28%), headache (25%)

*If >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine, max dose is 20 mg daily. BID = twice daily; CrCl = creatinine clearance; H1 = histamine; NaSSA = Noradrenergic and specific serotonergic antidepressant; PI = package insert; QHS = at bedtime; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TID = three times daily; $5HT_{1A}$ = serotonin

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Common Pharmacologic Agents to Consider for Anxiety and Trauma Related Disorder[21,22]							
Class	Agent	Initial Dose	Maximum Dose/Day	Guidance in Special Populations			Additional Information
				Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment	
SNRI	Duloxetine	30 mg DAILY	60 mg DAILY	20–40 mg DAILY	Avoid: CrCl <30 ml/min	Avoid	Headache (13–14%) somnolence (10–12%), nausea (23–25%), xerostomia (11–15%; dose related); avoid in patients with large ethanol intake, evidence of liver disease or hepatic impairment
	Venlafaxine IR	37.5 mg BID	225–375 mg	25–225 mg (2–3 divided doses)	CrCL 10–70 ml/min, ↓ dose 50%	↓ Dose 50%	Tremor (1–10%), hypertension (3% <100 mg/day, up to 13% >300 mg/day), asthenia (10% to 27%), dizziness (13% to 25%), feeling nervous (7% to 11%), headache (31%)
	Venlafaxine ER	75 mg DAILY	225 mg	37.5–225 mg DAILY	CrCL = 10–70 ml/min, ↓ dose 50%	↓ Dose 50%	

*If >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine, max dose is 20 mg daily. BID = twice daily; CrCl = creatinine clearance; H1 = histamine; NaSSA = Noradrenergic and specific serotonergic antidepressant; PI = package insert; QHS = at bedtime; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TID = three times daily; $5HT_{1A}$ = serotonin

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Common Pharmacologic Agents to Consider for Anxiety and Trauma Related Disorder[21,22]							
Class	Agent	Initial Dose	Maximum Dose/Day	Guidance in Special Populations			Additional Information
				Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment	
$5HT_{1A}$ Partial Agonist	Buspirone	7.5 mg BID	60 mg in divided doses BID-TID	No adjustment	Avoid in severe impairment	Avoid in severe impairment	Dizziness (3–12%), nausea (8%), somnolence (10%); wait 3–4 weeks before assessing response. Not effective as needed.
NaSSA	Mirtazapine	15 mg QHS	45 mg QHS	7.5–45 mg DAILY	CrCl <40 ml/min use caution	Titrate slowly	Drowsiness (54%), weight gain (12%), increased serum cholesterol (15%) xerostomia (25%), increased appetite (17%), constipation (13%)

*If >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine, max dose is 20 mg daily. BID = twice daily; CrCl = creatinine clearance; H1 = histamine; NaSSA = Noradrenergic and specific serotonergic antidepressant; PI = package insert; QHS = at bedtime; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TID = three times daily; $5HT_{1A}$ = serotonin

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Common Pharmacologic Agents to Consider for Anxiety and Trauma Related Disorder[21,22]							
Class	Agent	Initial Dose	Maximum Dose/Day	Guidance in Special Populations			Additional Information
				Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment	
TCA	Clomipramine	25 mg QHS	250 mg QHS	Avoid	Use with caution	Use with caution	Dizziness (54%), tachycardia (20%), orthostatic hypotension (20%), drowsiness (46%), xerostomia (84%), tremor (54%), constipation (47%), nausea (33%), ejaculation failure (42%) Contraindicated in seizure disorder

*If >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine, max dose is 20 mg daily. BID = twice daily; CrCl = creatinine clearance; H1 = histamine; NaSSA = Noradrenergic and specific serotonergic antidepressant; PI = package insert; QHS = at bedtime; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TID = three times daily; $5HT_{1A}$ = serotonin

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Common Pharmacologic Agents to Consider for Anxiety and Trauma Related Disorder[21,22]							
Class	Agent	Initial Dose	Maximum Dose/Day	Guidance in Special Populations			Additional Information
				Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment	
GABA Agonist	Gabapentin	300 mg DAILY	3600 mg in divided doses BID-TID	See Renal Dosing	CrCl 30–59 mL/min: 400–1400 mg CrCl 15–29 mL/min: 200–700 mg DAILY CrCl <15 mL/min: refer to PI	No adjustment	Dizziness (11–38%), somnolence (5–21%), peripheral edema (2–8%)

*If >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine, max dose is 20 mg daily. BID = twice daily; CrCl = creatinine clearance; H1 = histamine; NaSSA = Noradrenergic and specific serotonergic antidepressant; PI = package insert; QHS = at bedtime; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TID = three times daily; $5HT_{1A}$ = serotonin

continued

Common Pharmacologic Agents to Consider for Anxiety and Trauma Related Disorder[21,22]							
Class	Agent	Initial Dose	Maximum Dose/Day	Guidance in Special Populations			Additional Information
				Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment	
GABA Agonist	Pregabalin	75 mg BID	150 mg BID	See Renal Dosing	CrCl 30–60 mL/min: 75–300 mg CrCl 15–30 mL/min: 25–150 mg CrCl < 15 mL/min: 25–75 mg DAILY	No adjustment	Dizziness (8–45%), somnolence (4–36%), fatigue, peripheral edema (up to 16%)
H1 Antagonist	Hydroxyzine	25 mg TID-QID	100 mg DAILY	Avoid	No adjustment	Use once daily dosing	Tolerance may develop; associated with anticholinergic side effects; headache, somnolence

*If >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine, max dose is 20 mg daily. BID = twice daily; CrCl = creatinine clearance; H1 = histamine; NaSSA = Noradrenergic and specific serotonergic antidepressant; PI = package insert; QHS = at bedtime; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TID = three times daily; $5HT_{1A}$ = serotonin

Potential Contributors to Insomnia

Medications/Substances that Interfere with Sleep[23,24]		
Alcohol	Caffeine	Thyroid Hormone
Phenytoin	Central Nervous System Stimulants	Nicotine
Anticholinesterase Inhibitors	Decongestants (e.g. pseudoephedrine)	SSRIs/SNRIs
Bupropion	Diuretics	Theophylline

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor

Co-Morbid Conditions that Interfere with Sleep[23]			
Asthma	Chronic Pain Disorders (e.g. arthritis, neuropathic pain)	Irritable Bowel Syndrome	Epilepsy
COPD	Cardiac (e.g. congestive heart failure, angina)	Reflux (GERD)	Parkinsons Disease
Sleep Apnea	Hyperthyroidism	Nocturia	Restless Legs Syndrome
Psychiatric Disorders			
Substance Use	Anxiety Disorders	Depression	PTSD

COPD = Chronic Obstructive Pulmonary Disease; GERD = Gastroesophageal Reflux Disease; PTSD = Posttraumatic Stress Disorder

Cognitive Behavioral Therapy for Insomnia (CBT-I)

Effectiveness	• Effective intervention in up to 80% of insomnia patients who participate in CBT-I[25] • Improvements in sleep with CBT-I can be maintained years after therapy[25,26] • CBT-I is effective for chronic and severe insomnia
Goals of Treatment	• CBT-I is a multi-component treatment that addresses an individual's sleep-related behaviors • The primary goal is to improve sleep by deliberate and explicit efforts to modify irrational or dysfunctional thoughts, beliefs and expectations
Candidates	• If the Veteran is willing to try CBT for insomnia, enter a referral • Patients with co-morbid depression, PTSD, cancer, AUD, and chronic pain can benefit from CBT-I and should not be excluded from referrals
Notes	• Typically delivered over 5–6 sessions in individual or small group format[26,27] • CBT-I can be used alone or in combination with sedative hypnotics but some data suggests CBT-I alone is more effective[28]

AUD = alcohol use disorder; PTSD = posttraumatic stress disorder

Insomnia Medication Options

If the patient has been offered CBT-I and basic principles of sleep hygiene but is still suffering from insomnia, medications may be an option.

Recommended Dosing for Pharmacotherapy Alternatives to Benzodiazepines for Sleep[5,21,22,29,30]

Class	Agent	Usual Hypnotic Dose	Sedation Onset	Half-life	Guidance in Special Populations		
					Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment
TCA	Doxepin*	3–6 mg	~30 min	~15 hrs	Initial: 3 mg Max: 6 mg	N/A	Max: 3 mg
	Amitriptyline	10–25 mg	Not specified	9–27 hr	Avoid	N/A	Begin low and increase as tolerated

*Doxepin 10 mg can be considered as an alternative to the FDA approved dose approved for insomnia (3–6 mg) based on clinical judgment; **Use caution if taking prazosin; ***OTC, not available through the VA; ^Use caution if taking trazodone; +Do not use suvorexant with strong CYP3A Inhibitors (e.g. ritonavir) and use a max of 10 mg with moderate CYP3A inhibitors (e.g. diltiazem); ‡A variety of dosage strength and formulations of melatonin are available. NF = Not currently on VA National Formulary; PI = package insert; TCA = tricyclic antidepressant

continued

Recommended Dosing for Pharmacotherapy Alternatives to Benzodiazepines for Sleep[5,21,22,29,30]							
Class	Agent	Usual Hypnotic Dose	Sedation Onset	Half-life	Guidance in Special Populations		
					Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment
Anticonvulsant	Gabapentin	600–900 mg	Not specified	5–7 hr anuria: 132 hr	See Renal Dosage	CrCl 15–29 mL/min: 200–700 mg DAILY CrCl <15 mL/min: refer to PI	N/A

*Doxepin 10 mg can be considered as an alternative to the FDA approved dose approved for insomnia (3–6 mg) based on clinical judgment; **Use caution if taking prazosin; ***OTC, not available through the VA; ^Use caution if taking trazodone; +Do not use suvorexant with strong CYP3A Inhibitors (e.g. ritonavir) and use a max of 10 mg with moderate CYP3A inhibitors (e.g. diltiazem); ‡A variety of dosage strength and formulations of melatonin are available. NF = Not currently on VA National Formulary; PI = package insert; TCA = tricyclic antidepressant

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Class	Agent	Usual Hypnotic Dose	Sedation Onset	Half-life	Guidance in Special Populations		
					Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment
Antidepressant	Trazodone**	25–100 mg	1–3 hr	7–8 hr	Caution in elderly pts	N/A	N/A
	Mirtazapine	7.5–15 mg	Not specified	20–40 hr	Titrate slowly	CrCl <40 ml/min use caution	Titrate slowly

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					Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment
Antihistamine	Diphenhydramine	25–50 mg	1–3 hr	2–10	Avoid	bedtime dosing ok	N/A
	Doxylamine***	25 mg	~30 min	10–13	Avoid	N/A	N/A
	Hydroxyzine	10–100 mg	15–30 min	~20	Avoid	GFR <50 ml/min: ↓ dose 50%	N/A

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Class	Agent	Usual Hypnotic Dose	Sedation Onset	Half-life	Guidance in Special Populations		
					Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment
Melatonin Agonist	Melatonin[±]	0.5–5 mg	30 min	1.8–2.1	N/A	N/A	N/A
	Ramelteon (NF)	8 mg	~30 min	1–3	N/A	N/A	Mild: use caution Severe: not recommended

[*]Doxepin 10 mg can be considered as an alternative to the FDA approved dose approved for insomnia (3–6 mg) based on clinical judgment; [**]Use caution if taking prazosin; [***]OTC, not available through the VA; [^]Use caution if taking trazodone; [+]Do not use suvorexant with strong CYP3A Inhibitors (e.g. ritonavir) and use a max of 10 mg with moderate CYP3A inhibitors (e.g. diltiazem); [±]A variety of dosage strength and formulations of melatonin are available. NF = Not currently on VA National Formulary; PI = package insert; TCA = tricyclic antidepressant

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Class	Agent	Usual Hypnotic Dose	Sedation Onset	Half-life	Guidance in Special Populations		
					Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment
Alpha-1 Antagonist	Prazosin^ (trauma nightmares)	Initial: 1 mg Average: 9–13 mg	Not specified	2–3	Titrate slowly	N/A	N/A
Non-Benzodiazepines	Zolpidem IR	Women 5 mg Men 5–10 mg	~30 min	2.5	Max: 5mg Avoid use >90d	N/A	5 mg

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					Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment
Non-Benzodiazepines	Zolpidem CR	Women 6.25 mg Men 6.25–12.5 mg	~30 min	2.8	Max: 6.25 mg Avoid use >90d	N/A	6.25 mg
	Eszopiclone	1–3 mg	~10 mins	6	2 mg	N/A	2 mg

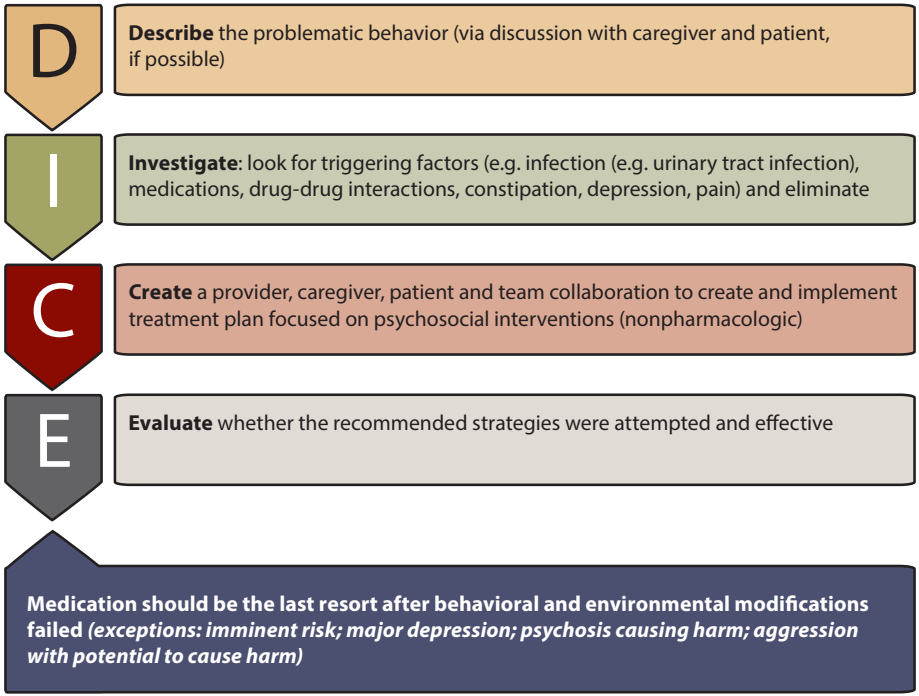
*Doxepin 10 mg can be considered as an alternative to the FDA approved dose approved for insomnia (3–6 mg) based on clinical judgment; **Use caution if taking prazosin; ***OTC, not available through the VA; ^Use caution if taking trazodone; +Do not use suvorexant with strong CYP3A Inhibitors (e.g. ritonavir) and use a max of 10 mg with moderate CYP3A inhibitors (e.g. diltiazem); ‡A variety of dosage strength and formulations of melatonin are available. NF = Not currently on VA National Formulary; PI = package insert; TCA = tricyclic antidepressant

continued

Recommended Dosing for Pharmacotherapy Alternatives to Benzodiazepines for Sleep[5,21,22,29,30]							
Class	Agent	Usual Hypnotic Dose	Sedation Onset	Half-life	Guidance in Special Populations		
					Geriatric (Dosage Range)	Renal Impairment	Hepatic Impairment
Non-Benzodiazepines	Zaleplon	5–10 mg	~30 mins	~1	Initial: 5 mg Max: 10 mg	N/A	Mild – moderate impairment: 5 mg Severe impairment: not recommended
Orexin Receptor Antagonist	Suvorexant[+] (NF)	10–20 mg	~30 mins	12	N/A	N/A	Severe impairment: not recommended

[*]Doxepin 10 mg can be considered as an alternative to the FDA approved dose approved for insomnia (3–6 mg) based on clinical judgment; [**]Use caution if taking prazosin; [***]OTC, not available through the VA; [^]Use caution if taking trazodone; [+]Do not use suvorexant with strong CYP3A Inhibitors (e.g. ritonavir) and use a max of 10 mg with moderate CYP3A inhibitors (e.g. diltiazem); [‡]A variety of dosage strength and formulations of melatonin are available. NF = Not currently on VA National Formulary; PI = package insert; TCA = tricyclic antidepressant

Treatment Guidelines for Behavioral and Psychological Symptoms of Dementia[31]



Pharmacologic Agents FDA-approved for Dementia[5,21,22,32]				
	Initial Dose	Titration	Max Dose	Comments
Cholinesterase Inhibitors and Memantine[*33–37]				
Donepezil	5 mg QHS	After 4–6 weeks	10 mg QHS+	Mild to severe dementia; Adverse effects: nausea, diarrhea, vomiting, bradycardia, syncope; NVD usually resolves in 1–3 weeks
Galantamine IR	4 mg BID IR	↑ by 8 mg after 4 weeks	24 mg daily	Mild to moderate dementia; Adverse effects: nausea, vomiting, diarrhea, dizziness
Galantamine ER	8 mg daily ER			

NF = Not on VA National formulary; NVD = nausea, vomiting, diarrhea; UTI = urinary tract infections; *Treatment with cholinesterase inhibitors and memantine is appropriate for those with possible or probable Alzheimer's disease diagnosis. Most evidence of efficacy is in patients with Alzheimer's disease or vascular dementia. +Max dose of donepezil 23 mg for patients with moderate to severe dementia who have a suboptimal clinical response to 10 mg at 3 months (23 mg is not currently on VA National Formulary).

continued

Pharmacologic Agents FDA-approved for Dementia[5,21,22,32]				
	Initial Dose	Titration	Max Dose	Comments
Rivastigmine Oral (NF)	1.5 mg BID	↑ by 1.5 mg BID every 2–4 weeks	12 mg	Lewy body dementia; may assist with visual hallucinations; Adverse effects: dizziness, weight loss, nausea, vomiting, diarrhea, anorexia; In patients <50 kg, monitor closely for toxicities (eg, excessive nausea, vomiting), and consider reducing the dose if such toxicities develop; If oral or patch is interrupted for ≤3 days, restart the treatment at the same or lower daily dose and titrate as previously described; If oral or patch interrupted >3 days, reinitiate at the initial start dose and increase patch no sooner than every 4 weeks. Apply patch on the next day following last oral dose; Smokers: polyaromatic hydrocarbons in tobacco smoke increases the clearance of rivastigmine by 23%.
Rivastigmine Patch	4.6 mg patch/ 24 hours	↑ to 9.5mg patch after 4 weeks	13.3 mg patch	

NF = Not on VA National formulary; NVD = nausea, vomiting, diarrhea; UTI = urinary tract infections; *Treatment with cholinesterase inhibitors and memantine is appropriate for those with possible or probable Alzheimer's disease diagnosis. Most evidence of efficacy is in patients with Alzheimer's disease or vascular dementia. +Max dose of donepezil 23 mg for patients with moderate to severe dementia who have a suboptimal clinical response to 10 mg at 3 months (23 mg is not currently on VA National Formulary).

continued

Pharmacologic Agents FDA-approved for Dementia[5,21,22,32]				
	Initial Dose	Titration	Max Dose	Comments
Memantine IR	5 mg	↑ by 5 mg weekly	10 mg BID	Moderate to severe dementia; Adverse effects: dizziness, confusion, hallucinations

NF = Not on VA National formulary; NVD = nausea, vomiting, diarrhea; UTI = urinary tract infections; *Treatment with cholinesterase inhibitors and memantine is appropriate for those with possible or probable Alzheimer's disease diagnosis. Most evidence of efficacy is in patients with Alzheimer's disease or vascular dementia. +Max dose of donepezil 23 mg for patients with moderate to severe dementia who have a suboptimal clinical response to 10 mg at 3 months (23 mg is not currently on VA National Formulary).

Pharmacologic Considerations for Behavioral Symptoms in Dementia[**5,21,22,32]				
	Initial Dose/Max Dose	Titration	Typical Range	Comments
Antidepressants[38–43]				
Citalopram	10 mg/ 40 mg[x]	weekly	10–30 mg	4 total RCTs for citalopram; Comparable to risperidone with improved tolerability; Safety: 1 RCT reported worsening cognitive function; QTc prolongation concerns
Sertraline	25 mg/ 200 mg	weekly	25–50 mg	1 RCT for sertraline; Comparable to haloperidol with less incidence of EPS

1st line treatment for behavioral symptoms in dementia should include behavioral interventions. If medications are required, clinical characteristics of the individual patient must be considered when weighing the risks versus benefits of each agent.
**Pharmacological agents presented in this table are off-label and not strongly supported by literature; [x]Maximum dose of citalopram 20 mg recommended for >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine; [^]Maximum dosing of prazosin was 2 mg qAM + 4 mg qPM. [#]Black box warning for serious and sometimes fatal dermatologic reactions. [*]The optimal dose of trazodone in geriatric patients is 150 mg. AChEI = acetylcholinesterase inhibitor; EPS = extrapyramidal symptoms; RCT = randomized controlled trial

continued

Pharmacologic Considerations for Behavioral Symptoms in Dementia[**5,21,22,32]				
	Initial Dose/Max Dose	Titration	Typical Range	Comments
Escitalopram	10 mg/ 20 mg	weekly	5–10 mg	1 RCT for escitalopram; Comparable to risperidone with improved tolerability
Fluvoxamine	50 mg/ 300 mg	weekly	25–200 mg	1 RCT for fluvoxamine; Comparable to risperidone with improved tolerability
Trazodone	25 mg/ 400 mg[*]	↑ by 50 mg 3–4 days	150 mg is optimal; range 50–300 mg	2 RCTs and 1 naturalistic follow-up study

1st line treatment for behavioral symptoms in dementia should include behavioral interventions. If medications are required, clinical characteristics of the individual patient must be considered when weighing the risks versus benefits of each agent.
**Pharmacological agents presented in this table are off-label and not strongly supported by literature; [x]Maximum dose of citalopram 20 mg recommended for >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine; [^]Maximum dosing of prazosin was 2 mg qAM + 4 mg qPM. [#]Black box warning for serious and sometimes fatal dermatologic reactions. [*]The optimal dose of trazodone in geriatric patients is 150 mg. AChEI = acetylcholinesterase inhibitor; EPS = extrapyramidal symptoms; RCT = randomized controlled trial

continued

Pharmacologic Considerations for Behavioral Symptoms in Dementia[**5,21,22,32]				
	Initial Dose/Max Dose	Titration	Typical Range	Comments
Miscellaneous[45–52]				
Buspirone	15 mg/ 60 mg In divided doses	↑ by 5 mg/ day every 2–3 days	15–60 mg with 30 mg target dose	1 RCT (single blinded); Improvement reported in delusion, aggression and anxiety
Gabapentin	300 mg/ 3600 mg In divided doses	↑ by 300 mg every 1–3 days	200–900 mg	7 case reports, 2 retrospective cases; Reduction in agitation/aggression reported Adjust dose if CrCl <60 mL/min

1st line treatment for behavioral symptoms in dementia should include behavioral interventions. If medications are required, clinical characteristics of the individual patient must be considered when weighing the risks versus benefits of each agent.
**Pharmacological agents presented in this table are off-label and not strongly supported by literature; ˣMaximum dose of citalopram 20 mg recommended for >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine; ^Maximum dosing of prazosin was 2 mg qAM + 4 mg qPM. #Black box warning for serious and sometimes fatal dermatologic reactions. *The optimal dose of trazodone in geriatric patients is 150 mg. AChEI = acetylcholinesterase inhibitor; EPS = extrapyramidal symptoms; RCT = randomized controlled trial

continued

Pharmacologic Considerations for Behavioral Symptoms in Dementia[**5,21,22,32]				
	Initial Dose/Max Dose	Titration	Typical Range	Comments
Carbamazepine[#]	100 mg/ 1200 mg In divided doses	↑ by 50 mg every 2–4 days	Mean dose 300–400 mg	2 RCTs and 1 non-randomized trial; May lead to reduction in aggression, agitation and/or hostility; Safety: 1 RCT reported worsening of hallucinations
Prazosin	1 mg QHS/No defined max[^]	↑ by 1 mg every 3–7 days	Mean dose 5–6 mg	1 RCT; Improvement reported in agitation/aggression; Safety: No effects on blood pressure revealed

1st line treatment for behavioral symptoms in dementia should include behavioral interventions. If medications are required, clinical characteristics of the individual patient must be considered when weighing the risks versus benefits of each agent.
[**]Pharmacological agents presented in this table are off-label and not strongly supported by literature; [x]Maximum dose of citalopram 20 mg recommended for >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine; [^]Maximum dosing of prazosin was 2 mg qAM + 4 mg qPM. [#]Black box warning for serious and sometimes fatal dermatologic reactions. [*]The optimal dose of trazodone in geriatric patients is 150 mg. AChEI = acetylcholinesterase inhibitor; EPS = extrapyramidal symptoms; RCT = randomized controlled trial

continued

Pharmacologic Considerations for Behavioral Symptoms in Dementia[**5,21,22,32]				
	Initial Dose/Max Dose	Titration	Typical Range	Comments
Vitamin E	1000 IU twice daily	1000 IU twice daily	1000 IU twice daily	2 RCT found vitamin E 1000 IU twice a day in combination with an AChEI significantly slowed progression in activities of daily living decline

1st line treatment for behavioral symptoms in dementia should include behavioral interventions. If medications are required, clinical characteristics of the individual patient must be considered when weighing the risks versus benefits of each agent.
**Pharmacological agents presented in this table are off-label and not strongly supported by literature; ^Maximum dose of citalopram 20 mg recommended for >60 years old, hepatic impairment, poor CYP 2C19 metabolizer or on cimetidine; ^Maximum dosing of prazosin was 2 mg qAM + 4 mg qPM. #Black box warning for serious and sometimes fatal dermatologic reactions. *The optimal dose of trazodone in geriatric patients is 150 mg. AChEI = acetylcholinesterase inhibitor; EPS = extrapyramidal symptoms; RCT = randomized controlled trial

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VA Academic Detailing Service

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This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint. These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

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Created August 2016

IB 10-929, P96811 **www.va.gov**