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Re-evaluating the Use of Second Generation Antipsychotics

A Quick Reference Guide

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Cardiometabolic Side Effects with Antipsychotic Use[3–12]				
Medication	**Metabolic Syndrome**	**Weight Gain**	**Glucose Dysregulation**	**Dyslipidemia**
Aripiprazole	+	+	++	+
Asenapine (NF)*	+	+	+	+
Clozapine	++++	++++	++++	++++
Iloperidone (NF)*	++	++	+	+
Lurasidone*	+	+	++	+
Olanzapine	++++	++++	++++	++++
Paliperidone (NF-Oral)*	++	++	+++	++
Quetiapine	+++	+++	+++	+++
Risperidone	++	++	+++	++
Ziprasidone	-/+	+	-/+	-/+

-/+ insignificant, + low, ++ moderate, +++ moderately high, ++++ high. *Newer medications do not have enough data to truly assess their effects on metabolic parameters; ratings are based on 6-week clinical trial data. Data indicates that treatment naive patients gain weight on even low risk medications. **NF = Not currently on VA National formulary.**

Dosing Recommendations for Atypical Antipsychotics[1,2]				
Medication	**Indication**	**Initial (mg)**	**Target (mg)**	**Maximum (mg)**
Aripiprazole	Depression -as adjunct to antidepressant	2–5	2–10	15
	Bipolar Disorder	10–15	15	30
	Schizophrenia	10–15	10–15	30
Asenapine (NF)	Bipolar Disorder	5–10 BID	5–10 BID	10 BID
	Schizophrenia	5 BID	5–10 BID	10 BID
Clozapine*	Schizophrenia	12.5 daily or BID	300–450	900

NF = Not currently on VA National formulary; *Requires slow titration to prevent orthostasis.

Additional Information

- **Dose-related adverse effects:** akathisia, sedation, extrapyramidal reaction, fatigue, sialorrhea, tremor.
- **Non dose-related adverse effects:** headache, anxiety, agitation, insomnia.
- Sublingual tablet; avoid use in severe hepatic impairment; **Adverse effects:** akathisia, drowsiness, insomnia, hypertriglyceridemia.
- **Black Box Warning:** orthostatic hypotension, seizures, cardiomyopathy, agranulocytosis, mortality in dementia-related psychosis. If >48 hours from last dose—retitrate from initial starting dose.

continued

Dosing Recommendations for Atypical Antipsychotics[1,2]				
Medication	**Indication**	**Initial (mg)**	**Target (mg)**	**Maximum (mg)**
Iloperidone* (NF)	Schizophrenia	1 BID	6–12 BID	12 BID
Lurasidone	Bipolar Depression	20	40–120	120
	Schizophrenia (NF)	40	40–80	160
Olanzapine*	Depression, in combination w/ fluoxetine	Olanzapine/ fluoxetine (NF*) (6/25)	6/25–12/50	Olanzapine/ fluoxetine (NF*) (12/50)
	Bipolar Disorder	10–15		20
	Schizophrenia	5–10	10	20

NF = Not currently on VA National formulary; *Requires slow titration to prevent orthostasis.
NF* = Combination product is not currently available on VA National Formulary. Therapeutic substitution using the individual products may be considered by the prescribing clinician.

Additional Information

- If >3 days of therapy missed—retitrate from initial starting dose; reduce dose by 50% with use of CYP2D6 and CYP3A4 inhibitors.
- Should be given with food (at least 350 calories); dose adjust in renal/hepatic impairment and with CYP3A4 inducers/inhibitors.
- **Adverse effects:** drowsiness, extrapyramidal reactions, fatigue, xerostomia, dizziness, increased serum prolactin, weight gain hypercholesterolemia, serum triglycerides raised.

continued

Dosing Recommendations for Atypical Antipsychotics[1,2]				
Medication	**Indication**	**Initial (mg)**	**Target (mg)**	**Maximum (mg)**
Paliperidone (NF-Oral)	Schizophrenia	6	3–12	12
Quetiapine*	Depression**	50	150–300	300
	Bipolar Disorder	50 daily –BID	400–800	800
	Schizophrenia	25 BID	150–750	800
Risperidone*	Bipolar Disorder	1–2	1–6	6
	Schizophrenia	1–2	4–8	16

NF = Not currently on VA National formulary; *Requires slow titration to prevent orthostasis.

Additional Information

- Requires dose adjustment in renal impairment (CrCl <80 mL/min).
- Lower initial dose in hepatic impairment; dose adjust with strong CYP3A4 inducers/inhibitors; **As Adjunct to antidepressant, XR only.
- **Adverse effects:** parkinsonian-like syndrome, weight gain, drowsiness, headache, tremor, hyperprolactinemia.
- Risperidone maximum recommended dosing per FDA is 16 mg but doses >8 mg associated with more adverse effects. Doses >6 mg/day do not appear to be more effective.

continued

Dosing Recommendations for Atypical Antipsychotics[1,2]				
Medication	**Indication**	**Initial (mg)**	**Target (mg)**	**Maximum (mg)**
Ziprasidone	Bipolar Disorder	40 BID	40–80 BID	80 BID
	Schizophrenia	20 BID	20–80 BID	80 BID

Additional Information

- Should be given with at least 500 calories; recommend baseline EKG prior to initiation and periodically. Although minor QTc prolongation (mean: 10 msec at 160 mg/day) may occur more frequently (incidence not available), clinically-relevant prolongation (>500 msec) was rare.

Evidence of Antipsychotic Use in Anxiety Disorders and Depression

Summary of Strength of Evidence of Efficacy, by Drug and Condition[13–15]						
		Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety	Generalized Anxiety Disorder			**Response NNT = 8**		
	Social Phobia					
OCD	Augmentation of SSRI				**Response NNT = 5**	
Depression	MDD Augmentation of SSRI/SNRI				**Remission NNT = 8 Response NNT = 7**	
	Monotherapy			**Remission NNT = 13 Response NNT = 6**		

OCD = Obsessive Compulsive Disorder
MDD = Major Depressive Disorder
SSRI = Selective Serotonin Reuptake Inhibitor
SNRI = Serotonin-Norepinephrine Reuptake Inhibitor

Evidence of Efficacy (EE)

- High or moderate
- Low or very low
- Evidence of inefficacy
- No trials

Differentiating PTSD Symptoms from Psychosis[16,17,18]

It is important to differentiate **PTSD symptoms** from **psychosis.**

Approach to Assessing Psychosis

- Comprehensive assessment of psychotic symptoms
- Observe for concurrent thought disorder
- Assess affect
- Rule out substance use, intoxication, withdrawal
- New onset psychosis requires full evaluation including medical workup

continued

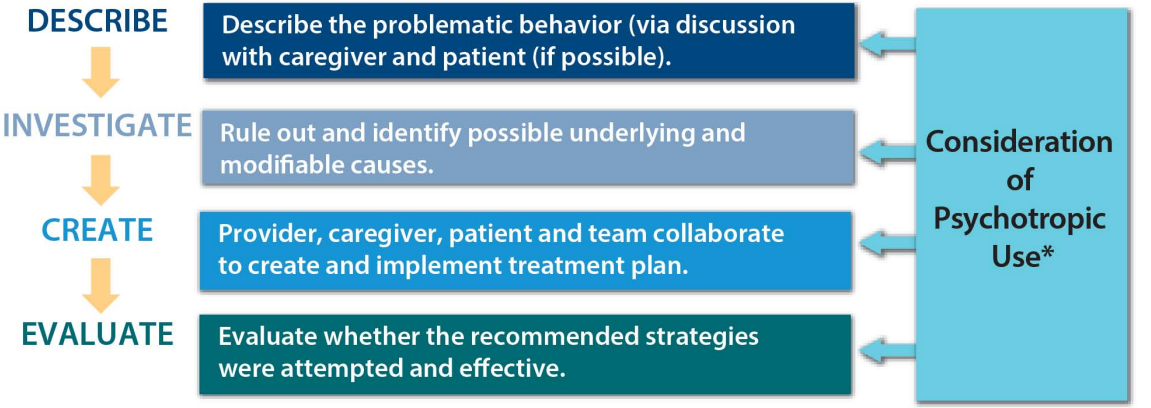
Consistent with PTSD

- Feeling of mistreatment or mistrust
- Always looking over shoulder, expecting something bad to happen (hyperarousal/hypervigilance)
- Misinterpreting cues: seeing something out of corner of their eye, hearing a sound in the house at night and interpreting it as an intruder
- Hearing voices or seeing deceased only at night with decreased visual cues (also vision or sensory impaired Veterans)
- In moments of strong affect (anger) at a person, having intrusive violent images
- Experiencing flashback of reliving an experience

Consistent with Psychosis

- Not confined to episodes of re-experiencing, but remain present continuously and often paranoid in nature
- Examples:
  - Believing that his/her family needed to die to protect them from evil
  - Believing that his/her house is bugged by the government
  - Leaving home and barricading oneself into a hotel room for fear that his/her military role in Vietnam would be discovered by spouse placing him/her at risk of being killed
  - Hearing voices telling Veteran he/she is bad or evil

Non-Pharmacologic Considerations for Behavioral Symptoms in Dementia[19]



*Consensus recommendations suggest psychotropics should be used only after significant efforts are made to reduce non-cognitive neuropsychiatric symptoms using behavioral and environmental modifications and medical interventions if needed. Three exceptions were noted due to concerns for significant and imminent risk:

1. Major depression with or without suicidal ideation;
2. Psychosis causing harm or with great potential of harm; and
3. Aggression causing risk to self or others.[19]

Adapted from: Kales et al. Management of Neuropsychiatric Symptoms of Dementia in Clinical Settings: Recommendations from a Multidisciplinary Expert Panel.

Pharmacologic Agents FDA-Approved for Dementia[1,2,20,21,22]				
	Initial Dose	Titration	Max Dose	Comments
Cholinesterase Inhibitors and Memantine*[23–27]				
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	↑ by 8 mg after 4 weeks	24 mg daily	Mild to moderate dementia; Adverse effects: nausea, vomiting, diarrhea, dizziness
Galantamine ER	8 mg daily	↑ by 8 mg after 4 weeks	24 mg daily	Mild to moderate dementia; Adverse effects: nausea, vomiting, diarrhea, dizziness

NF = Not currently 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 is 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[1,2,20,21,22]				
	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
Rivastigmine *patch*	4.6 mg patch/ 24 hours	↑ to 9.5 mg patch after 4 weeks	13.3 mg patch	If dosing is interrupted for ≤3 days, restart the treatment at the same or lower dose and titrate as previously described. Apply patch on the next day following last oral dose; smokers: nicotine increases the clearance of rivastigmine by 23%
Memantine IR	5 mg	↑ by 5 mg weekly	10 mg BID	Moderate to severe dementia; Adverse effects: dizziness, confusion, hallucinations

NF = Not currently 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 is 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**[1,2,20–22]				
	Initial/Max Dose	Titration	Typical Range	Comments
Antidepressants[28–33]				
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
Escitalopram	10 mg /20 mg	weekly	5–10 mg	1 RCT for escitalopram; comparable to risperidone with improved tolerability
Fluvoxamine (NF)	50 mg /300 mg	weekly	25–200 mg	1 RCT for fluvoxamine; comparable to risperidone with improved tolerability

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

continued

Pharmacologic Considerations for Behavioral Symptoms in Dementia**[1,2,20–22]				
	Initial/Max Dose	**Titration**	**Typical Range**	**Comments**
Trazodone	25 mg / 400 mg*	↑ by 50 mg every 3–4 days	50–300 mg	2 RCTs and 1 naturalistic follow-up study
Miscellaneous [34–40]				
Buspirone	15 mg / 60 mg in divided doses	↑ by 5 mg / day every 2–3 days	15–60 with 30 mg target dose	1 RCT (single blinded); improvement reported in delusion, aggression and anxiety
Gabapentin	300 mg / 3,600 mg in mg divided doses	↑ by 300 mg every 1–3 days	200–900 mg	7 case reports, 2 retrospective cases; reduction in agitation/aggression reported

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

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Pharmacologic Considerations for Behavioral Symptoms in Dementia**[1,2,20–22]				
	Initial/Max Dose	Titration	Typical Range	Comments
Carbamazepine[#]	100 mg / 1,200 mg in mg 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

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

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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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