Management of Neuropsychiatric Symptoms of Dementia
(UptoDate accessed 9/5/17)

Neuropsychiatric symptoms are common in dementia and lead to greater functional and cognitive impairment. Neuropsychiatric symptoms of dementia include delusions, hallucinations, depression, anxiety, euphoria, aggression, apathy, irritability, disinhibition, wandering or pacing, and sleep disturbances. Agitation, hallucinations, depression, and aggression in patients with dementia often lead to nursing home placement

- Treatment guidelines suggest identifying precipitating factors and to rule out/treat a medical cause or superimposed delirium
- Nonpharmacologic interventions have been shown to be effective for dementia-related behavioral problems and should be tried first when appropriate
- Pain is an important source of behavioral disturbances and should be managed using a stepped care approach (starting low & titrating slowly)
- A trial of selective serotonin reuptake inhibitors (SSRIs) is suggested for the treatment of depression in Alzheimer disease
    - Citalopram is often used for its possible additional benefits for other neuropsychiatric symptoms (MDD: 20 mg in elderly clts)
    - Sertraline is a well-studied alternative to citalopram
    - TCAs should be avoided because of side effects and drug interactions
- Consider a trial of dextromethorphan quinidine in clts with refractory agitation
- Antipsychotics have limited efficacy & are associated with increased mortality in patients with dementia
    - In case of severe, disabling symptoms, and/or threatening patient/caregiver safety despite safer interventions; consider low doses of olanzapine or risperidone after informing families of the mortality risk
    - Use short term when possible, with regular reassessments of risks and benefits
    - Clts with dementia with Lewy bodies (DLB) are at especially high risk of severe side effects with neuroleptic medications. When pharmacotherapy is necessary for treatment of behavioral symptoms, only very low doses of certain atypical neuroleptics (eg, quetiapine or clozapine) should be used

Acetylcholinesterase inhibitors help improve memory by increasing acetylcholine (ACh) levels at the synapse. Memantine, an NMDA (glutamate) receptor antagonist, works theoretically by preventing neurotoxicity from overstimulation of NMDA receptors

- Limited efficacy
    - Controlled studies indicated modest symptomatic benefit for cognition, mood, behavioral symptoms, and daily function in patients with Alzheimer's disease compared to placebo
        - About 10%–25% patients taking a cholinesterase inhibitor may show modest global improvement, but greater percentage may have less rapid cognitive decline
- Safety
    - Side effects include nausea, vomiting, diarrhea, bradycardia (galantamine 1%, rivastigmine <1%), and syncope
    - Memantine may cause constipation, dizziness, headache, and confusion
    - Acute gastrointestinal events (mostly nausea and vomiting) are class effects of all AChEIs, reported mostly during dose-escalation (more with dual AChE/BuChE inhibitor rivastigmine)

        - Minimized when administered with food
    - Starting at low doses with slow titration reduces side effects
- Attempt a taper as the client's condition permits to prevent chronic use of possibly unnecessary medications
- Consider removing/adjusting possible causative medications. Review medication interactions

Recommendations for AchEIs & memantine based on clinical practice and existing evidence:

- Trial with an AChEI for clts with mild to moderate dementia
    - Comparable efficacy, consider donepezil, rivastigmine, or galantamine based upon individual tolerance/cost
- AchEIs on average produce small improvements in cognition and activities of daily living. Not all clts benefit, impact on long-term outcomes, disability and institutionalization, remains unclear
    - Most studies have been in patients with AD, some evidence of benefit for patients with vascular dementia (VaD), mixed dementia, DLB, and dementia in PD. Consider a treatment trial of an AchEI in these clts as well, if needed
- Clts with dementia may also benefit from memantine and other therapies
- In clts with severe dementia, consider tapering AchEIs over a two to four week period. Treatment may be re-started if the clt worsens without the medication
- In clts with mild cognitive impairment (MCI) if memory problems are particularly troubling to the patient, consider a trial for symptomatic benefit

Medication induced delirium & confusional states	**Psychosocial interventions for management of behavioral & psychotic symptoms in patients with dementia**
o Prescription medications (eg, opioids, sedative-hypnotics, antipsychotics, lithium, skeletal muscle relaxants, polypharmacy) o Non-prescription medications (eg, antihistamines - diphenhydramine, hydroxyzine) o Drugs of abuse (eg, ethanol, heroin, hallucinogens, nonmedicinal use of prescription medications) o Withdrawal states (eg, ethanol, benzodiazepines) o Medication side effects (eg, hyperammonemia from valproic acid, confusion from quinolones, serotonin syndrome)	o Routine activity o Separate the person from what seems to be upsetting him/her o Assess for the presence of pain, constipation or other physical problem o Review medications, especially new medications o Travel with them to where they are in time o Don't disagree; respect the person's thoughts even if incorrect o Physical interaction: Maintain eye contact, get to their height level, and allow space o Speak slowly and calmly in a normal tone of voice. The person may not understand the words spoken, but he or she may pick up the tone of the voice behind the words and respond to that o Avoid finger-pointing, scolding or threatening. o Redirect the person to participate in an enjoyable activity or offer comfort food he or she may recognize and like o If you appear to be the cause of the problem, leave the room for a while o Validate that the person seems to be upset over something. Reassure the person that you want to help and that you love him or her o Avoid asking the person to do what appears to trigger an agitated or aggressive response

Medication Options	Comments
Antidepressants	○ Depression may affect about one fourth of Alzheimer's patients, its associated with wandering, agitation, and aggression ○ Evidence of antidepressant benefit for depression is conflicting ○ Antidepressants are relatively well-tolerated compared to antipsychotics ○ SSRIs esp citalopram (even at doses of 10 to 20 mg daily) is useful in the management of agitation and paranoia. Citalopram should be avoided in patients at increased risk for arrhythmias and discontinued if persistent QTc >500 ms ○ May overlap with an antipsychotic (eg, quetiapine) in the first few weeks (SSRI may require weeks to demonstrate effect) ○ Sertraline has the most data for the treatment of depression in Alzheimer's patients, it may also improve behavior/functioning, and reduce caregiver stress. Consider initial dose of 25 mg daily, increasing by 25 mg weekly to a max daily dose of 150 mg ○ Limited evidence suggests trazodone may improve agitation, irritability, and depression. Concern for sedation, falls, & hypotension
Atypical Antipsychotics	○ Increased risk of mortality in elderly patients with dementia (1 more death for every 50 to 100 dementia patients over 8 to 12 weeks) ○ Reserve for clts with agitation or psychosis that is severe, significantly distressing, or causes the clt to act in a way that creates a danger to themselves or others ○ Use 1/3 to 1/2 the usual initial dose, or the smallest strength available, titrate to the lowest effective dose. Limit to a 4-week trial. If no clinically significant response, taper by no more than 50% every 2 weeks & discontinue ○ Aripiprazole, risperidone, and olanzapine have the best efficacy evidence ○ Risperidone is Health Canada-approved for aggression and psychosis in severe AD ○ Reserve haloperidol for emergency situations eg. acute delirium ○ In the absence of clear differences in efficacy, medication selection is primarily based on SEs & individual clt characteristics ○ Clts with DLB may be especially sensitive to antipsychotics and may experience idiosyncratic, life-threatening AEs. Very low doses of atypicals (eg, quetiapine, clozapine) should be used. Risperidone & the typical antipsychotics should not be used
Cholinesterase Inhibitors and/or Memantine	○ Efficacy in the treatment of neurobehavioral symptoms is not strong ○ Well tolerated & may have additional benefit for cognition and function ○ Consider starting an AchEI for clts with neuropsychiatric sx and mild to moderate dementia ○ Clts with DLB may have a better response to AchEIs than clts with AD (greater cholinergic deficit in DLB than in AD) ○ The potential efficacy of memantine to improve the behavioral effects in AD requires further study (see recommendations for AchEIs & memantine below)
Drugs with uncertain benefit **Anticonvulsants (mood stabilizers)**	○ Low-dose carbamazepine (300 to 400 mg/d) seems effective, but limited evidence. Many DDIs, requires lab monitoring ○ Open-label data suggests efficacy for lamotrigine. Main side effects are potentially serious rash, dizziness, ataxia, vision disturbance, sedation, nausea/vomiting ○ Current evidence does not support efficacy of valproate for agitation in patients with dementia. Cognitive changes, falls, sedation, & other serious side effects. Requires lab monitoring
Medications with possible benefit	○ Potential benefit for melatonin and/or light therapy in patients with dementia, lack of convincing benefit for agitation

	○ Low doses of methylphenidate are often helpful for apathy but can precipitate agitation; requires careful monitoring
Dextromethorphan 20 mg / quinidine 10 mg (Nuedexta)	○ FDA approved approved for symptomatic treatment of pseudobulbar affect ○ Dextromethorphan blocks NMDA receptors and quinidine boosts dextromethorphan levels ○ Limited evidence suggests that it may provide some benefit for severe agitation in patients with dementia ○ Many DDIs and potential for serotonin syndrome ○ Serious adverse effects include falls and QT prolongation
Drugs to avoid	○ Benzodiazepines have limited value & are not recommended for the management of neuropsychiatric symptoms of dementia ○ Reserve for acute crisis (agitation, severe anxiety, stressful episodes, or an anxiety-provoking medical event). Benzos with shorter half-lives should be preferred ○ SEs include worsening gait, potential paradoxical agitation, & possible dependence ○ Antihistamines are discouraged due to high rates of side effects, particularly for medications with anticholinergic effects, such as diphenhydramine

FDA-Approved Medications for Alzhiemer's Disease

(Treatment Guidelines from The Medical Letter, Vol. 11, Issue 134, October 2013)

Drug	Formulations	Usual Dosage	Starting Dose/Titration	Cost[1]
Acetylcholinesterase Inhibitors				
Donepezil – generic	5, 10, 23 mg tabs	5-10 mg once/d	5 mg once/d; after 4-6 wks	$9.00
Aricept (Eisai/Pfizer)			increase to 10 mg once/d; if	353.00
orally disintegrating – generic	5, 10 mg orally		suboptimal response to 10 mg	50.00
Aricept ODT (Eisai/Pfizer)	disintegrating tabs		after 3 months, can consider increasing to 23 mg	353.00
Galantamine – generic	4, 8, 12 mg tabs;	16-24 mg divided	8 mg/d divided bid; after 4 wks	146.00
Razadyne[2] (Janssen)	4 mg/mL soln	bid with meals	increase to 16 mg/d, then after 4 wks more to 24 mg/d	241.00
extended-release – generic	8, 16, 24 mg ER caps	16-24 mg once/d	8 mg once/d; after 4 wks	140.00
Razadyne ER (Janssen)		with meals	increase to 16 mg/d, then after 4 wks more to 24 mg/d	241.00
Rivastigmine – generic	1.5, 3, 4.5, 6 mg caps	9-12 mg divided	3 mg/d divided bid; increased	164.00
Exelon (Novartis)	1.5, 3, 4.5, 6 mg caps; 2 mg/mL soln	bid with meals	in increments of 3 mg/d q 2 wks[3] to 12 mg/d	285.00
transdermal				
Exelon Patch (Novartis)	4.6 mg/24 hours, 9.5 mg/24 hours, 13.3 mg/24 hours	9.5 mg/24 hours	4.6 mg/24 hours; after 4 wks increase to 9.5 mg/24 hours; after an additional 4 wks increase to 13.3 mg/24 hours	296.00
NMDA-Receptor Antagonist				
Memantine –	5, 10 mg tabs;	10 mg bid	5 mg once/d; increase in	
Namenda (Forest)	2 mg/mL soln		increments of 5 mg q wk to 20 mg/d divided bid	265.00
extended-release				
Namenda XR (Forest)	7, 14, 21, 28 mg ER caps	28 mg once/d	7 mg once/d; increase to 28 mg/d in increments of 7 mg q wk	252.00

ODT = orally disintegrating tablet; ER = extended release

1. Approximate cost for 30 days' treatment with the lowest usual dosage. Source: Source® Monthly (Selected from FDB MedKnowledge™) September 5, 2013. Reprinted with permission by FDB, Inc. All rights reserved. ©2013. www.fdbhealth.com/policies/drug-pricing-policy. Actual retail prices may be higher.
2. Formerly *Reminyl*.
3. Every 4 weeks for dementia associated with Parkinson's disease.

		Donepezil Aricept	Rivastigmine	Galantamine	Memantine
Indications		Mild, moderate, or severe dementia of the Alzheimer type (all stages)	<u>Alzhiemer Dementia</u> PO- Mild to moderate TD- Mild, moderate or severe <u>Parkinson disease Dementia</u> Mild to moderate	Mild to moderate dementia of AD	Moderate to severe dementia of the Alzheimer type
Off label uses		Dementia related to PD, Lewy body dementia	Lewy body dementia	Severe AD, Dementia associated with PD, Lewy body dementia	Vascular dementia
MOA		Cholinesterase inhibitor	Cholinesterase & butyrylcholinesterase inhibitor	Cholinesterase inhibitor, modulation of cholinergic nicotinic receptors	Antagonist of NMDA type of glutamate receptors
Hepatic dose adjustment		No	PO: Recommended (severe hepatic impairment: not studied) TD: Yes (severe hepatic impairment: not studied)	Yes	Use with caution
Renal dose adjustment		No	PO: Recommended TD: None	Yes	Yes
PK/ PD	Metabolism T1/2 (h)* Tmax (h) Excretion	Hepatic T1/2: 70 Tmax: dose dependent Mostly Urine	Hydrolysis in the brain T1/2: PO- 1.5, Patch- 3 (after removal) Tmax: PO- 1, TD: 8-16 following 1st dose Urine	Hepatic T1/2: 7 Tmax: IR- 1 (2.5 with food); ER- 4.5-5 Urine (20%)	Partially hepatic T1/2: 60-80 Tmax: IR 3-7, ER 9 to 12 Mostly urine
Monitoring parameters		Mental status, weight, GI intolerance sx, GI bleeding sx. Monitor for cholinergic crisis	Cognitive function at periodic intervals, GI intolerance sx, weight Monitor for cholinergic crisis	Mental status, weight Monitor for cholinergic crisis	Cognitive function, periodic ophthalmic exams, HTN, CNS changes, rash & constipation
Warnings		May be associated w/ altered cardiac conduction, rhabdomyolysis, & NMS. May cause bradycardia, anorexia/weight loss (dose-related), diarrhea, N/V Use with caution in clts at risk of ulcer disease, respiratory disease, seizure disorder, & urinary tract obstruction	May cause allergic dermatitis, CNS depression, EPS, GI effects (dose related, more frequent in women), & bradycardia. Use w/ caution in clts w/ PUD, respiratory disease, seizure disorder, & urinary tract obstruction	May cause CNS depression, skin reactions, bradycardia, & weight loss Use w/ caution in clts with cardiac conduction abnormalities, hepatic/renal impairment, PUD, respiratory disease, seizure disorder, & urinary tract obstruction	Use with caution in clts w/ CV disease, hepatic/renal, ophthalmic disease, seizure disorder, & conditions which may alter urine pH

	Some products may contain aspartame, avoided in patients with phenylketonuria			
Major SEs	N/V, diarrhea, syncope abdominal pain, insomnia, infection, accidental injury, bradycardia	N/V, diarrhea, syncope, dizziness, agitation, abdominal pain, tremor, headache, fall, weight loss	N/V, diarrhea, syncope decreased appetite/ weight loss	Dizziness/ confusion headache, HTN diarrhea, constipation
Other notable SEs	HTN, pain, dizziness, weight loss, ecchymosis, ECG abnormality	HTN, fatigue, depression, confusion	Dizziness (falling) headache, depression, fatigue, tremor, bradycardia	Influenza, back pain, cough ER: anxiety, weight gain, depression
Clinical pearls	Start with 5 mg daily to decrease incidence of side effects Dose-related diarrhea, N/V usually resolves in 1 to 3 weeks Clts weighing <55 kg may experience more N/V & weight loss	If GI side effects with capsules, hold several doses & restart at same or lower dose if treatment is interrupted for >3 days, reinstate at the lowest daily dose (1.5 mg BID) Systemic exposure may be increased in clts <50 Kg & decreased in clts >100 Kg Significant DDIs: may enhance bradycardic effect of beta-blockers & AEs of metoclopramide (EPS). Nicotine increases rivastigmine clearance by 23% TD formulation causes fewer GI AEs compared to oral, can cause rash, rotate sites Patch can be used if dysphagia or a G-tube	If stopped for >3 days, restart at lowest dose Limited safety data in clts ≥85 yo. Use with caution specifically clts with low weight or serious comorbidities	May be used with AChEIs. If treatment is stopped for longer than several days, restart with a lower dose
	• Transitory effects on delaying clinical deterioration, does not stop or reverse the underlying neurodegenerative process • Namzaric, a fixed dose combination of ER memantine and donepezil was FDA approved in 2014 for treatment of moderate to severe Alzheimer's type dementia in patients previously stabilized on both drugs • Studies needed to determine if adding memantine to an AChEI is more effective than an AchEI (mixed study results) • Administer rivastigmine & galantamine with meals			

DLB: Dementia with Lewy bodies, NMDA: N-methyl-D- aspartate, *(h): hours, sx: symptoms,
PUD: Peptic Ulcer Disease, NMS: Neuroleptic Malignant Syndrome