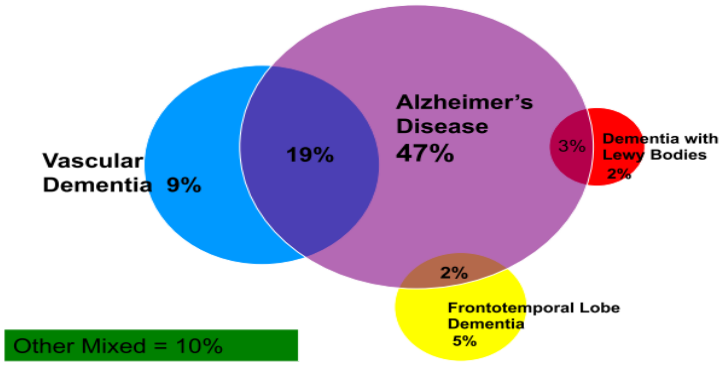
DSM-V CRITERIA FOR NEUROCOGNITIVE DISORDERS:

- Significant cognitive decline in ≥ 1 cognitive domain
  - Ex// complex attention, executive function, learning & memory, language, perceptual-motor, or social cognition
  - Based on: concern of individual or other, impairment in cognitive performance, preferably documented by testing
- Cognitive deficits interfere with independence in everyday activities (if NO – mild)
- Cognitive deficits do not occur exclusively with delirium
- Cognitive deficits are not better explained by another mental disorder
- Specify etiology: Alzheimer's disease, vascular disease, frontotemporal lobar degeneration, Lewy body disease, PD, substance use, HIV

ETIOLOGY:



CONTRAINDICATIONS AND PRECAUTIONS:

ChEI	• Peptic ulcer disease • Hepatic or renal disease • Significant bradycardia, AV block, SSS, unexplained syncope • Significant bronchopastic disease • Obstructive urinary disease • Epilepsy, hx of seizures or drug interactions
Memantine	• Hypersensitivity • Caution in seizure hx or disorder; cardiovascular disorder

INTERACTIONS:

ChEI	PD interactions	• Anticholinergic drugs (oxybutynin, TCAs, some antipsychotics) • Bradycardic drugs (BB, CCBs, amiodarone, digoxin)
	PK interactions	• CYP3A4 inhibitors (erythromycin, clarithromycin, amiodarone, diltiazem, verapamil, ketoconazole, alprazolam, clonazepam) • CYP 2D6 inhibitors (fluoxetine, paroxetine, quinidine, thioridazine) • Hepatic microsomal enzyme inducers (alcohol, AEds, rifampin)
Memantine	• Urinary alkalizers may decrease clearance of memantine	

DOSING:

Donepezil	5 mg OD x 4-6 wks, then 10 mg OD	• Give in morning if causing insomnia • High dose (23 mg po) may be benefit in mod-sev dementia
Rivastigmine	1.5 mg BID x ≥ 2 wks, then 3 mg BID ≥ 2 wks, then 4.5 mg BID x ≥ 2 wks, then 6 mg BID 2 mg/mL oral solution, 4.6 mg/24h (patch 5), 9.5 mg /24h (patch 10), 13.3 mg/24 h (patch 15)	• Give with morning & evening meals • Food increases bioavailability • High dose (patch 15) patch may be benefit in mod-sev dementia
Galantamine	8 mg OD x 4 wks, then 16 mg OD x 4 wks, then can consider 24 mg OD	• ER formulation
Memantine	5 mg week 1 → 5 mg bid week 2 → 10 mg + 5 mg week 3 → 10 mg bid	• Reduce to 10 mg/d if GFR 30—49 mL/min ○ 10 mg BID if well tolerated after > 7 d • Do not use if GFR < 9 mL/min

EVALUATING SYMPTOMS:

- Interview
- sMMSE, MoCA
- Lab testing, imaging

INCREASED RISK OF INCIDENT ALZHEIMER'S DEMENTIA WITH CONTINUED USE OF ANTICHOLINERGIC MEDICATION OVER A 3.5 YEAR PERIOD

PHARMACOTHERAPY OF DEMENTIA:

Cholinesterase inhibitors	Donepezil	Mild to severe AD
	Rivastigmine PO	Mild to mod AD & PD
	Rivastigmine patch	Mild to severe AD
	Galantamine	Mild to moderate AD
NMDA receptor antagonist	Memantine	Mod to severe AD

EFFICACY:

- For treatment of dementias, cholinesterase inhibitors and memantine can improve sx (primarily cognitive & global function)
- Many cases of dementia have more than one condition contributing to causation = manage based on those other diagnoses (believed to be predominant contributing cases)

ALZHEIMER'S DISEASE:

- Most common cause of dementia
- Gradual onset and continuing decline of memory (and at least one other cognitive domain)

ChEIs	• All 3 demonstrated efficacy for mild to severe AD • Recommend trial for most patients with AD
Memantine	• Option for moderate stages of AD ○ Use in mild stages of AD not recommended • Benefit of treatment demonstrated in mod-sev AD • Use if ChEI intolerable
Combo	• Insufficient evidence for or against combo of ChEI and memantine • Add memantine for more cognitive benefits

DEMENTIA WITH LEWY BODIES:

- Core features: fluctuating cognitive impairment, recurrent visual hallucinations, parkinsonism

ChEIs	• Benefit for cognition and behavior • Case report of worsening of parkinsonism

PARKINSON DISEASE DEMENTIA:

ChEIs	• Recommended as treatment option • Benefit for cognition & global assessment

FRONTOTEMPERAL DEMENTIA:

- Behavioral changes: disinhibition, social conduct, emotional blunting
- Language impairment: progressive aphasia, semantic problems
- Relative memory sparing

Rivastigmine	• Improved behavioral measures
Donepezil	• May worsen FTD behaviors
Galantamine	• Not beneficial for behavioral variety of FTD

VASCULAR DEMENTIA (VaD):

ChEIs	• Insufficient & inconsistent evidence to make recommendation for or against

PK AND PD:

Drug	Donepezil	Rivastigmine	Galantamine	Memantine
F	100%, not affected by food	36% (food delays absorption)	90% (IR affected by food, ER not)	100% (unknown effect of food)
PPB	96%	40%	18%	45%
Metabolism	CYP2D6, 3A4	Hydrolysis	CYP2D6, 3A4	No CYP
T ½	70 h	1-2 h	7-8 h	60-100 h
Elimination	Unknown for renal fxn, ↓ with liver cirrhosis	↓ with hepatic impairment, unknown for renal fxn	Do not use with severe hepatic or renal impairment	Unchanged in urine; dose adjust with reduced renal fxn
Inhibits	AChEI	AChEI, BuChEI	AChEI, nicotinic	

STOPPING THERAPY:

- Patient/proxy decision maker
- Pt refuses or is sufficiently non-adherent
- Rate of decline (cognitive, function, behavior) is greater on txt compared to prior
- Intolerable side effects
- Co-morbidities make continued use unacceptably risky or futile
- Dementia progresses to a stage where no clinically meaningful benefit from continued therapy

Monitor patient after stopping therapy. If significant decline in cognition, functional abilities or development / worsening of behavioral changes, consider reinstating.

ADHERENCE:

- Stopping and restarting = no benefit & may lose any initial gains
- May be 6-12 weeks of continuous therapy before benefit is seen

BEHAVIORAL AND PSYCHOLOGICAL SX OF DEMENTIA (BPSD):

- Maybe medication responsive:
  - Anxiety, restlessness
  - Sadness
  - Insomnia
  - Withdrawn, apathetic
  - Verbal & physical aggression
  - Delusions, hallucinations
  - Sexually inappropriate behavior
- Probably not medication responsive
  - Wandering
  - Inappropriate dressing/undressing
  - Repetitiveness
  - Hiding/hoarding
  - Eating inedibles
  - Inappropriate isolation
  - Removal of restrains

ADVERSE EFFECTS:

ChEI	• CNS: abnormal dreams, insomnia, agitation, depression, dizziness, headache
	• RESP: pneumonia
	• CVS: syncope, bradycardia
	• GI: nausea, vomiting, diarrhea, anorexia, malaise, abdominal pain
	  ○ NV: consider lower dose, with food, caregiver administer, stop drug
	  ▪ Antiemetics may have anticholinergic effects
	• MSK: muscle & leg cramps, falls, injury, hip fracture (donepezil!)
	
	Discontinue if disabling or dangerous. If minor, decrease dose and can retry higher dose after 2-4 weeks if lower dose tolerated.

Memantine	• Generally well-tolerated • Dizziness, headache, confusion, constipation, nausea, vomiting • May be an increase in agitation and delusions/hallucinations

OTHER DRUG THERAPY OPTIONS?

Ginkgo biloba	Efficacy	• Questionable • Non-regulated
	Safety	• Concerns
Estrogens	Efficacy	• Compelling epidemiological data • Disappointing intervention trials
Anti-inflammatory agents	Efficacy	• Epidemiological evidence for lower AD incidence • Intervention studies do not support use
	Safety	• Prohibitive SE profile
Vitamin E	Efficacy	• One RCT showed delayed progression of AD with high doses • Slow functional decline in mild to mod AD
	Safety	• Concerns about mortality with use of high dose vit E
Souvenaid	Rationale	• Nutrition to help with formation of new synapses, compensating for that which has been lost
	Efficacy	• Improvement in verbal recall for early AD (not yet taking meds)
Coconut oil	Rationale	• Increased ketones may improve cognition • Axona (caprylidene) marketed as medical food in US, evaluated in mild-moderate AD

DRUG THERAPY FOR BPSD:

ChEIs	• Maybe beneficial for paranoia, delusions hallucinations, aggression, agitation, anxiety, disinhibition
SSRIs (sertraline, citalopram)	• Depression, agitation
Trazadone	• Agitation, aggression
Memantine	• Mean NPI reduction of -1.99 ??
Antidepressants	• Major depressive disorder • Severe dysthymia • Severe emotional liability
Antipsychotics (risperidone, olanzapine, aripiprazole)	• Potentially useful for delusions, hallucinations, aggression, agitation, and sleep disturbance • Benefits vs. risks (cerebrovascular events, mortality)