

The 3Ds – Delirium, Dementia, and Depression

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Objectives

At the conclusion of this presentation, attendees should be able to:

1. Define and distinguish the main characteristics of the 3D Geriatric Syndromes: Dementia, Delirium, and Depression
2. List the underlying risk factors and most common causes of the 3Ds
3. List the medications and their potential side-effects most commonly used to treat the 3Ds
4. Describe the most effective non-pharmacologic strategies to manage the 3Ds

Speaker Disclosures

Dr. Kumar has no relevant financial relationship(s).

Dr. Kumar will present the off-label use of antipsychotics and other psychotropic medication/therapy for delirium and behaviors in dementia. Note that this has not been approved by the FDA.

Case

Mr. DL is an 84 y/o cis-gender male with dementia for the past 5 years, who is newly admitted to LTC due to increasing aggressive behaviors and hallucinations over the past few weeks. His spouse reports that his confusion will change throughout the day, seemingly worse in the afternoons and evenings. At times, he appears despondent and tells his spouse that he is worthless and wants to die. At other times, he is very sleepy. He is restless at night and sleeps poorly. He has fallen multiple times in the last year and his spouse is worried for his safety.

What is the underlying cause of his recent condition change?

- Advancing dementia of Lewy Body Disease
- Mixed delirium due to an unrecognized medical condition
- Depression with psychosis
- I have no idea how to tell the difference



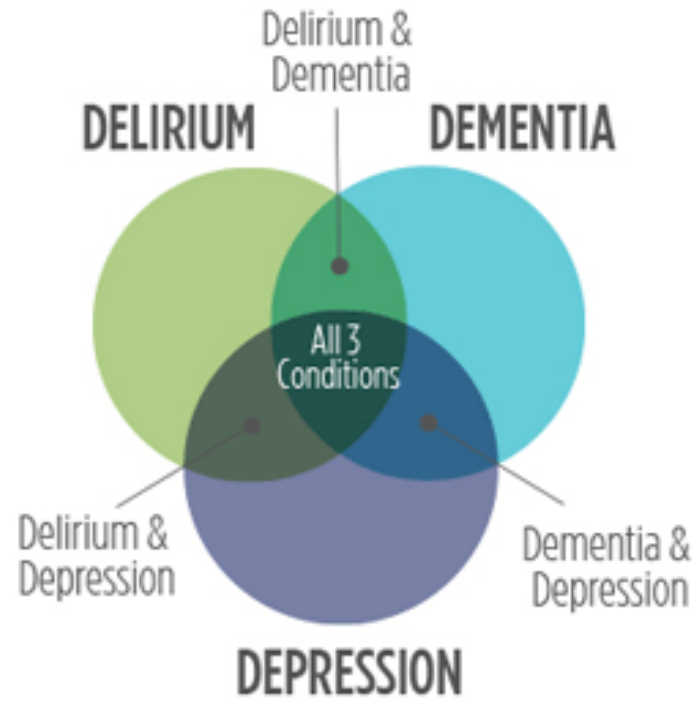
Which D?



The “Three Ds” Geriatric Syndromes



Acute change in mental status



Cognitive decline due to brain disease



Change in mood with feelings of worthlessness



Are there “normal” changes in memory with age?

Yes!!

- Slower recall of information, such as names
- Increased effort needed to learn new tasks
- Occasional forgetfulness - May rely more on lists, calendars, and reminders
- Greater difficulty multi-tasking
- Easier distractibility
- Slower processing

BUT, dementia is NOT NORMAL in the older adult



Cognitive Disorders: Warning Signs



Asking the same questions over and over again, repeating self often

Getting lost in familiar places

Inability to follow directions

Getting dates, people, or places mixed up

Problems with self-care, nutrition, hygiene, or safety

Unexplained weight loss or failure to thrive

Medication non-adherence

YOUR HEALTH

Treating Delirium: An Often Missed Diagnosis

Not all old age confusion is dementia



A Picture of ICU Delirium



© Peter E. Spronk – Geire Hospitals ICU, Apeldoorn, the Netherlands
Miriam B. Spronk (design)

Delirium

Sudden and frightening onset of
confusion



Delirium

Difficulty answering questions

Don't make sense

May hallucinate

May be very agitated

Different personality

Hospital care is complex and fragmented.

DELIRIUM IS...

**TRANSIENT, FLUCTUATING,
GLOBAL DYSFUNCTION
OF COGNITION**

DELIRIUM IS NOT...

DEMENTIA

DEPRESSION

ONLY AGITATION

Table 3. Comparison of hypo- and hyperactive delirium [58].

Feature	Hypoactive	Hyperactive
Arousal	Decreased arousal and alertness; somnolence; reduced awareness	Hypervigilant; easily startled; distractable
Mood	Depressed, irritable; mood swings; patient is disinhibited	Labile: from comatose to euphoric
Psychomotor activity	Slow, quiet, withdrawn	Restless, agitated, combative, irritable
Past psychiatric history	May have experienced delirium before	Correlated with alcohol or drug withdrawal; may have experienced delirium before
Circadian rhythm	Increased daytime sleepiness	Prominent disturbances; nightmares and night terrors

Or Mixed!



Hypoactive delirium has a worse prognosis with longer LOS and higher mortality

Is it Delirium or Dementia?

Condition	Time Course	Distinguishing Features
Delirium	Acute onset, fluctuating, lasting days to weeks (though could be longer)	Impaired attention Altered level of consciousness
Dementia	Progressive worsening, permanent	Unimpaired attention and level of consciousness until severe stages

However, there are features that are common in both:

Disorientation

Sleep-wake cycle reversal

Memory impairment

Hallucinations

Misdiagnosis of dementia common in SNF patients and rates range from 18% to 85%.

Briesacher BA, et al. Am Geriatr Soc 68:2931-2936, 2020.

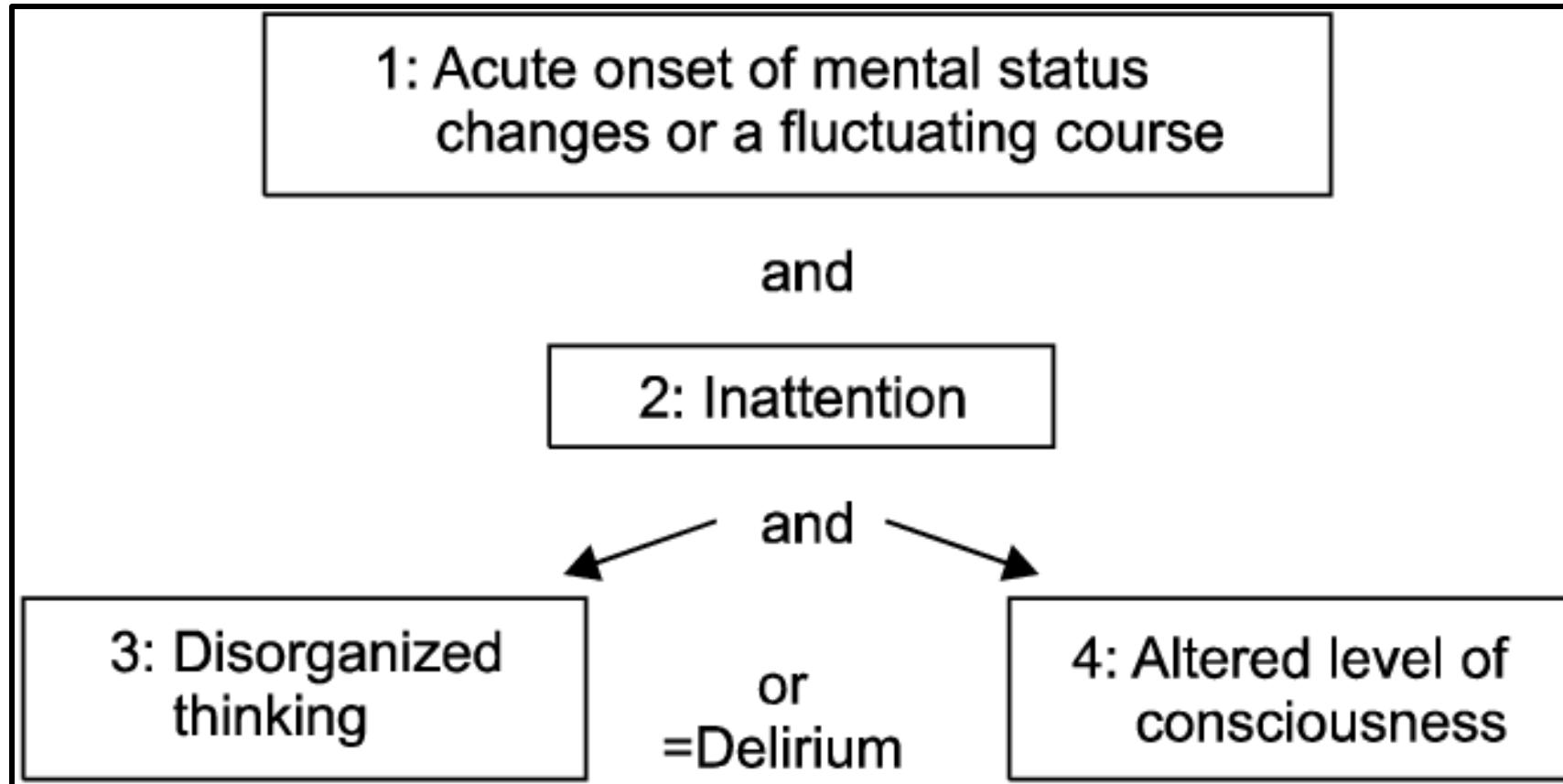
Delirium Can Also Look Very Much Like Depression

- 60% dysphoric
- 52% thoughts of death or suicide
- 68% feel “worthless”
- Up to 42% of cases referred for psychiatry consult services for *depression* are *delirious*
- *Consider catatonia in your delirium differential*



Bottom line: if you can't distinguish between the 3Ds based on clinical presentation, you must first rule out and work-up for **delirium: a dangerous diagnosis.**

Diagnosing Delirium



Video example



Precipitants of Delirium

- D** Drugs
- E** Eyes, Ears (sensory deprivation)
- L** Low O₂ States (MI, Stroke, PE, COPD exacerbation, organ failure)
- I** Infection
- R** Retention (Urine or Feces)
- I** Ictal (often absence)
- U** Underhydration, Undernutrition, Uncontrolled pain
- M** Metabolic (hypo/hyper-natremia, -calcemia, - thyroid, - glycemia; AKI)
- S** Subdural

Cystocerebral Syndrome* (Urinary Retention)

Symptoms: pain, agitated

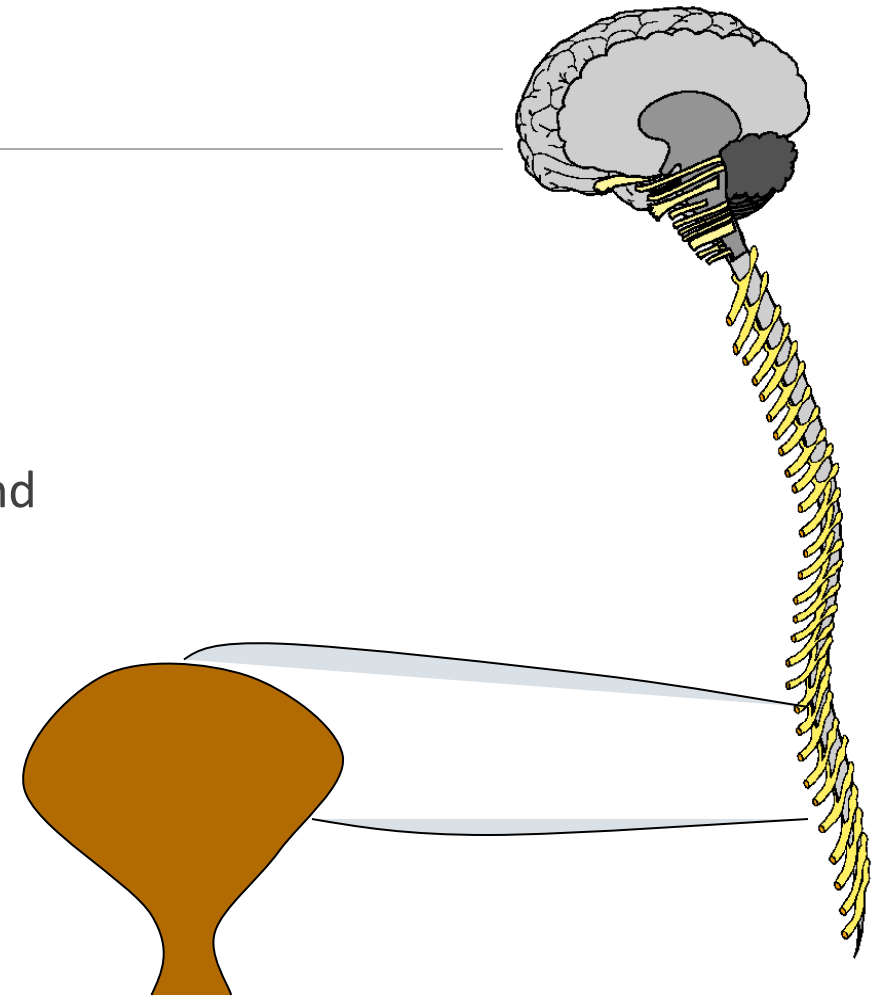
delirium, overflow incontinence,

acute renal failure

Well-established relationship between urinary retention and delirium but what about UTI and delirium?

Blackburn & Dunn, Arch Int Med 1990

Krinitski D, et al. J Am Geriatr Soc. 2021;69:3312–3323



UTI, ASB, and Delirium: Thorn in Geriatrician's Side

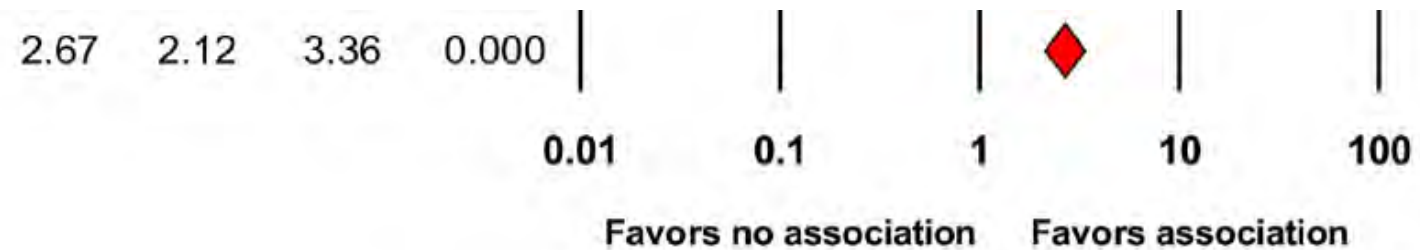


FIGURE 2 Forest plot of the main meta-analysis of 29 studies^{20–23,32–56} expressing associations between delirium and UTI in older adults. 95% CI, 95% confidence interval

The association between delirium and AB in older adults in the only study reporting this association that we could find was statistically insignificant: OR 1.62; 95% CI 0.57–4.65; p-value 0.37.

Bottom line: Bacteriuria in the absence of focal urinary symptoms should not be considered an infection and should not automatically prompt treatment with antibiotics to treat delirium.

Drugs that can cause an ACUTE CHANGE IN MS

ANTIPARKINSON **C**V DRUGS **I**NSOMNIA **M**MUSCLE Relaxants
Corticosteroid **H**₂ BLOCKERS **N**SAIDS **S**EIZURE
URIN INCONT **A**NTIBIOTICS
THEOPHLLYINE **N**ARCOTICS
EMPTYING DRUGS **G**ERO-PSYCH
ENT



Delirium in Older Adults

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Managing Delirium

LIMITED DATA IN PALTC

Table 1. Interventions to prevent delirium

Risk factor	Interventions
Cognitive impairment or disorientation	<ul style="list-style-type: none">» Provide an environment with clear signage and tools that can orient the person to time, such as a calendar or clock that is in clear sight» Verbally orient the person to time, place, person and who you are» Encourage visits from the person's family and friends
Suboptimal nutrition	<ul style="list-style-type: none">» Monitor the person's fluid intake and output closely to prevent dehydration» Work with a nutritionist to increase the person's fluid and food intake if necessary» If possible, provide the person's favourite foods and drinks» If the person uses dentures, ensure they fit well and are well maintained
Risk of infection	<ul style="list-style-type: none">» Monitor the person closely for infections and treat these promptly
Limited mobility	<ul style="list-style-type: none">» Encourage the person to undertake range of motion exercises, even if they are unable to walk» Provide the person with appropriate walking and mobilisation aids, if necessary» Post-surgery, encourage mobilisation as soon as possible
Pain	<ul style="list-style-type: none">» Observe the person for non-verbal signs of pain such as wincing or guarding, so that the pain can be managed as soon as possible» Manage pain using the most appropriate pharmacological and non-pharmacological interventions» Reassess pain regularly and adjust pain management interventions as required
Sleep disturbances	<ul style="list-style-type: none">» Provide a low-noise environment during sleep periods» Maintain a healthy sleep-wake schedule» Where possible, schedule medication administration and medical procedures at times that do not disrupt the person's sleep-wake schedule
Polypharmacy	<ul style="list-style-type: none">» Ensure regular reviews of the person's medications by a pharmacist to modify dosages where necessary

(National Institute for Health and Care Excellence 2019)

Management of Delirium: Pharmacologic

- Management of sleep-awake cycle: Melatonin 3-5 mg po QHS or Ramelteon 8 mg po QHS
 - Mixed evidence
 - Best evidence is for delirium prevention in ICU and perioperative settings
- Management of severe agitation:
 - **Antipsychotics do NOT prevent, shorten the duration of, or improve delirium**
 - Antipsychotics can protect patients when they are in imminent danger of harming themselves or others
 - Start with low doses and taper off as symptoms resolve (within 24-48 hours)
- Avoid benzodiazepines except in BDZ or ETOH withdrawal or if suspected catatonia

Han Y, et al. J Pineal Res. 2020 May;68(4):e12644. doi: 10.1111/jpi.12644. Epub 2020 Mar 25.

Campbell AM, et al. BMC Geriatr. 2019 Oct 16;19(1):272. doi: 10.1186/s12877-019-1297-6.

Ng KT, et al. J Clin Anesth. 2020 Feb;59:74-81. doi: 10.1016/j.jclinane.2019.06.027. Epub 2019 Jul 3.

Zhang Q, et al. Sleep Breath. 2019 Dec;23(4):1059-1070. doi: 10.1007/s11325-019-01831-5. Epub 2019 May 22.

Oh ES, et al. Ann Intern Med. 3 September 2019 [Epub ahead of print]. doi:10.7326/M19-1859

Nikooie R, et al. Ann Intern Med. 3 September 2019 [Epub ahead of print]. doi:10.7326/M19-1860

Stuck Between a Rock and a Hard Place

Haloperidol 0.25-3 mg per day (start 0.25-0.5 mg and titrate)

- Doses >4.5 mg/d → more EPS

Risperidone 0.5-3 mg/d, particularly for DSD

Quetiapine 25-300 mg/d for parkinsonism (lower risk EPS)

Benzodiazepines are to be avoided EXCEPT in withdrawal

Trazodone 25-200 mg/d

- Small study of palliative care patients with cancer, median daily dose 37.5 mg (25-50 mg/d)
- Reduced delirium severity and well tolerated (sedation common)

Dementia

Definition of Dementia

Memory impairment plus a decline in one or more cognitive domains—learning ability, social function, visuo-spatial function, language, complex attention, executive functioning

Significant decline from previous abilities

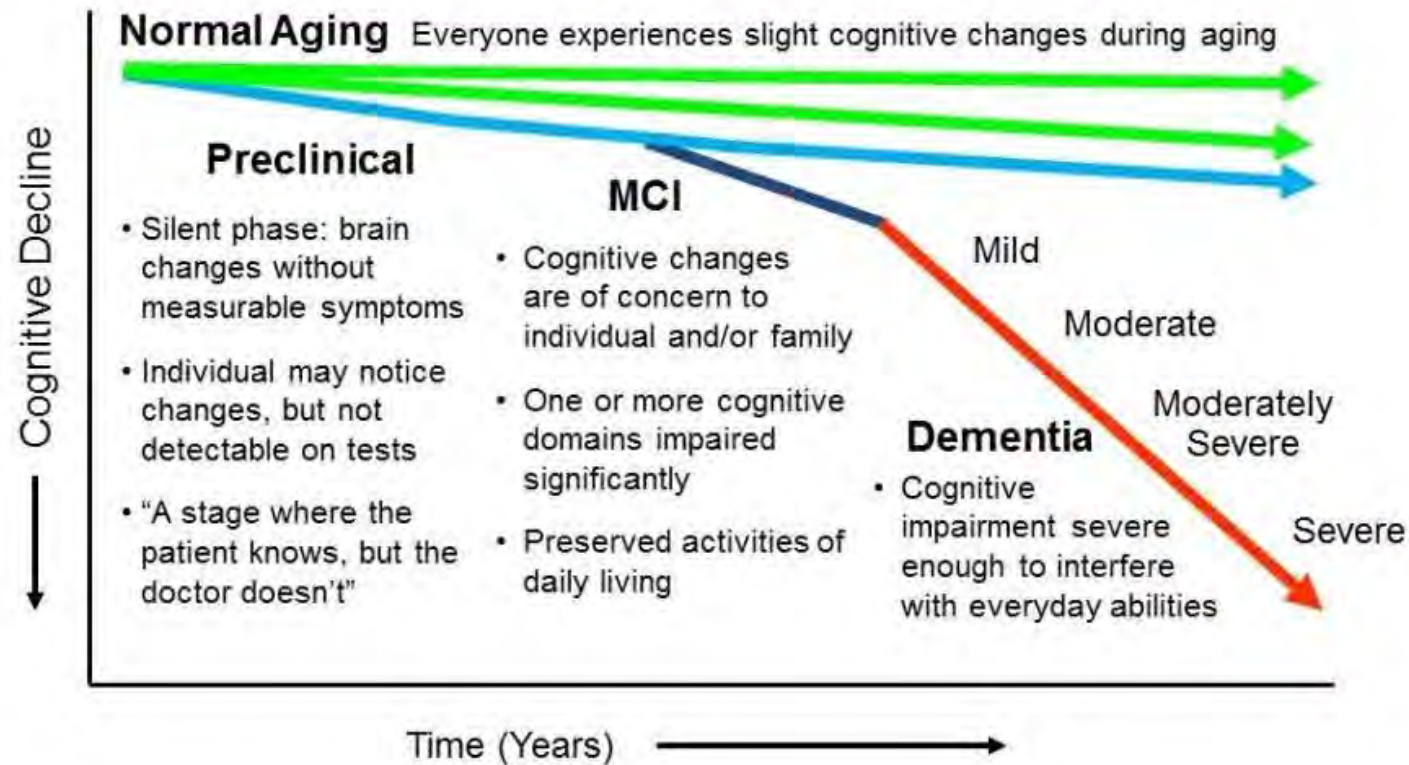
+Impairment in daily functioning

Decline is progressive, disabling

Caused by damage to the brain



3 stages in the development and progression of Dementia

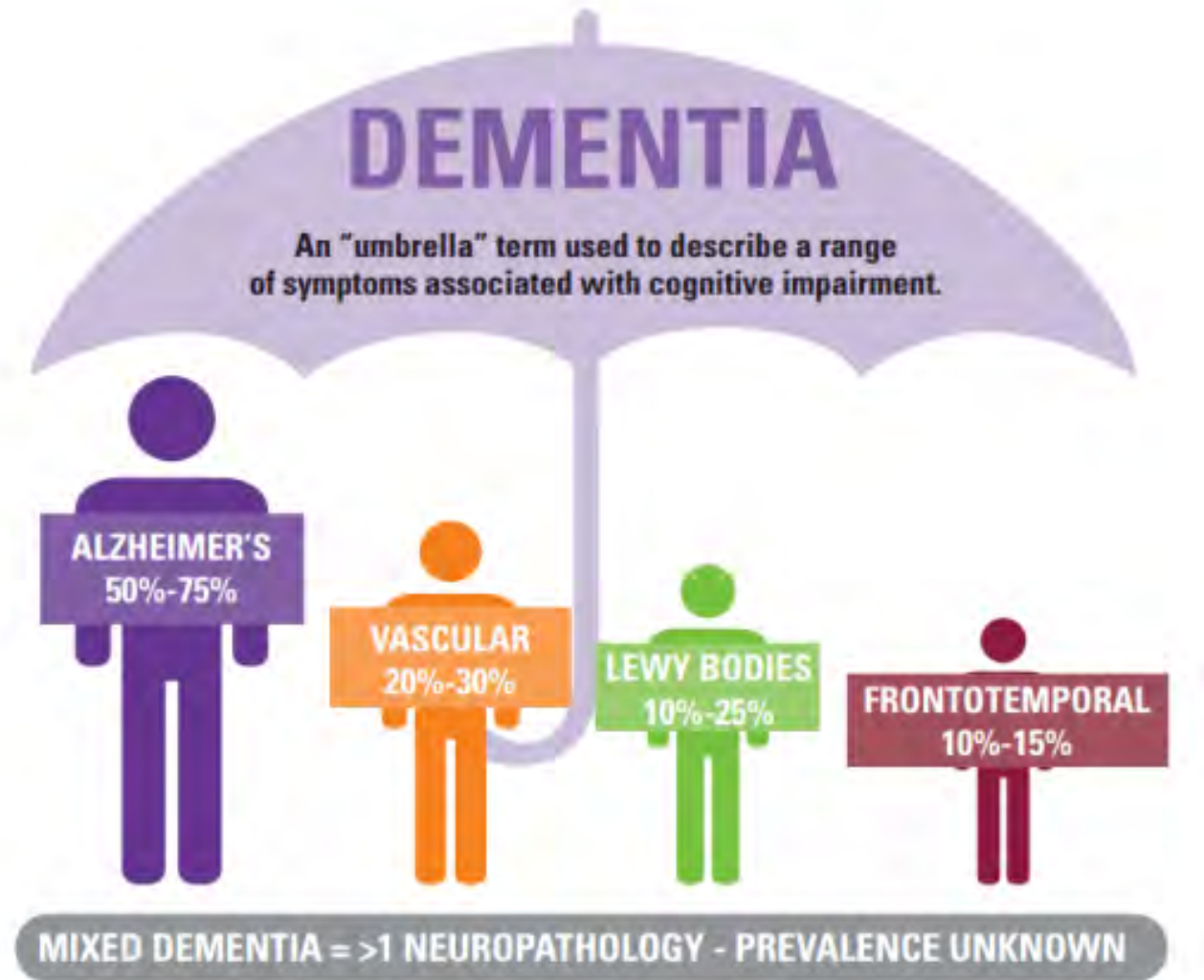


Impairment	Mild (1)	Moderate (2)	Severe (3)
Memory	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented in time, often to place	Oriented to person only
Judgment and problem	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside of home; appears well enough to be taken to functions outside of family home	No pretense of independent function outside of home; appears too ill to be taken to functions outside a family home
Home and hobbies	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal care	Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

NOT ALL DEMENTIA IS ALZHEIMER'S DISEASE

Diagnosis Goals:

- Rule out reversible causes!
- Distinguish between the various types of dementing illnesses
- Build a comprehensive treatment plan (bio-psycho-social care) tailored to the individual



Common Dementias in Older Persons

Reversible Causes

Alzheimer's disease (hyperamyloidosis)

Hippocampal sclerosis of aging

Primary age-related tauopathy (PART)

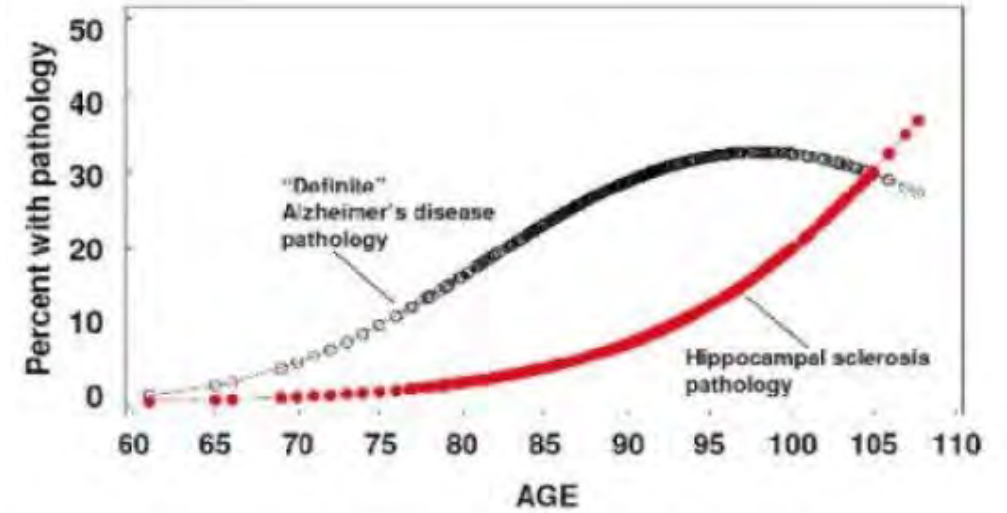
Vascular dementia

Frontotemporal Dementia

Limbic-predominate Age-related TDP-43 Encephalopathy (LATE)

Lewy body dementia (other Parkinsonian)

Dementia of Diabetes



Nelson PT1, et al. Brain. 2011 May;134(Pt 5):1506-18.

Reversible causes of MCI/Dementia

Drugs

Emotional (depression)

Metabolic (hypothyroidism, B12)

Eyes and ears (sensory isolation)

Normal Pressure Hydrocephalus (ataxia, incontinence, and dementia)

Tumor or other space-occupying lesion

Infection (syphilis, chronic infections)

Atrial fibrillation/Alcoholism

Sleep Apnea

~10 % of all Dementias



Diagnosis

Complete medical history

Physical and neurological examinations

- “Memory Test” → bedside screening tool

Neuroimaging

Laboratory tests

Neuropsychological assessment (optional)

****At the present time, there is no single diagnostic test for detecting mild cognitive impairment, Alzheimer’s Disease or other types of dementia**

Detecting MCI

Which of the following dementia screening tools can also be used to screen for MCI?

1. Mini Mental Status Examination (MMSE)
2. Saint Louis University Mental Status Examination (SLUMS)
3. Montreal Cognitive Assessment (MoCA)
4. Mini-Cog Test
5. Rapid Cognitive Screen (RCS)
6. All of the Above

Treatment of Dementia

There are **no proven cures or disease-slowing treatments...yet**

Goal is to **maximize cognitive abilities** for as long as possible (improve symptoms)

Medications only work in a small subset of patients and on average improve memory test scores by 1-2 points

There are **6 FDA approved medications:**

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)
- Memantine (Namenda)
- Aducanumab (Aduhelm) and lecanemab (Leqembi)*

*monoclonal Ab targeting amyloid protein, FDA approval 6/2021 and 1/2023, respectively

Generic Name	Brand Name	Dosage Forms	Mechanism	Starting Dosage	Goal Dosage
Donepezil	Aricept	IR tablet ODT	Cholinesterase inhibitor	5 mg/day	10 mg/day
Galantamine	Razadyne	IR tablet ER tablet	Cholinesterase inhibitor	4 mg bid or 8-12 mg/day	8 mg/day (ER) 16-24 mg/day (ER)
Memantine	Namenda	IR tablet	NMDA inhibitor	5 mg/day	10 mg bid
Rivastigmine	Exelon	Patch IR capsules Oral solution	Cholinesterase inhibitor	4.6 mg per 24 h 1.5 mg bid	9.5 mg per 24 h 6 mg bid

IR: immediate release; ODT: orally disintegrating tablet; ER: extended release; NMDA: N-methyl-D-aspartate (glutamate).

Is the person taking the medication for one of the following reasons:

ChEIs (donepezil, rivastigmine or galantamine):

- Alzheimer's disease, dementia of Parkinson's disease, Lewy body dementia or vascular dementia.

Memantine:

- Alzheimer's disease, dementia of Parkinson's disease or Lewy body dementia.

Donepezil: 5mg, 10 mg

Rivastigmine capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg

Rivastigmine patch (24h): 4.6 mg, 9.5mg , 13.3mg

Galantamine CR capsule: 8mg, 16mg, 24 mg

Memantine: 10 mg, 20 mg

Acetylcholinesterase Inhibitors (ChEI)

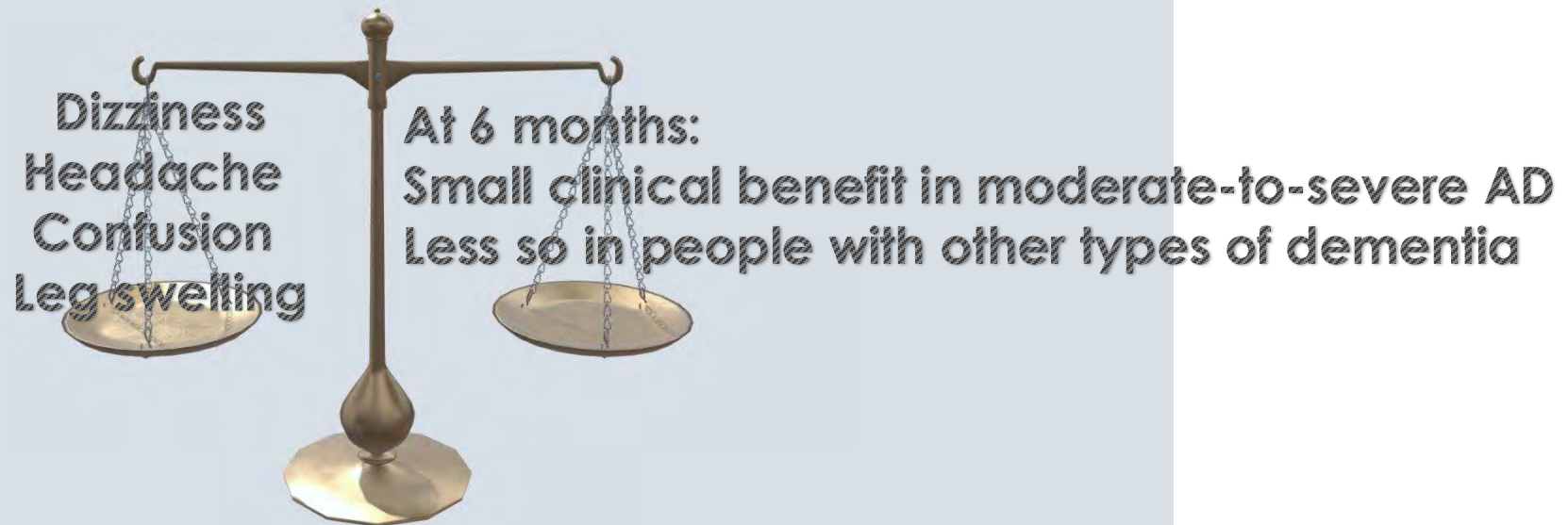
Diarrhea
Nausea
Weight loss
Dizziness
Headache
Fatigue
Bad Dreams
Incontinence
Passing out*
Heart block*
Low heart rate*
Seizures



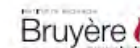
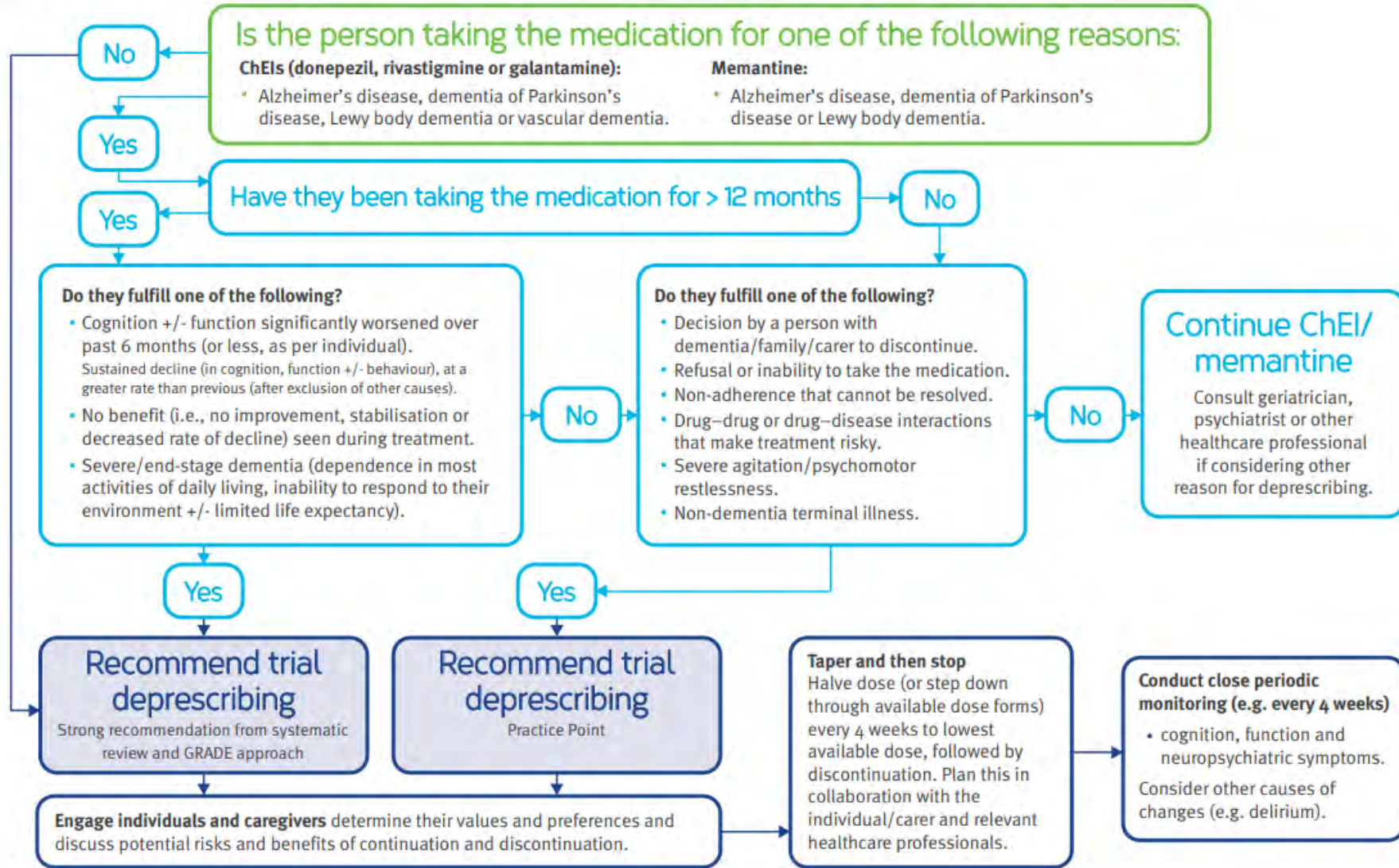
"Get worse less fast" (2-12 months)
Statistical versus meaningful change?
Best in early to moderate stage

*Caution when using medications that can lower heart rate, like metoprolol or diltiazem

Memantine



**Memantine + ChEI is no better than
ChEI alone or memantine alone**



Drugs That Impair Cognition

Anticholinergic

- Antiarrhythmic
- Antidepressants
- Antiemetics
- Antihistamine (1st generation)
- Antimuscarinics (urinary incontinence)
- Antiparkinsonian agents
- Antipsychotics
- Antispasmodics
- Muscle relaxants

Benzodiazapines (and Z-hypnotics)

Anticonvulsants

Opioids

Alcohol

Table 7. Drugs With Strong Anticholinergic Properties

Antiarrhythmic	Promethazine
Disopyramide	Pyrilamine
	Tripolidine
Antidepressants	
Amitriptyline	
Amoxapine	
Clomipramine	Antimuscarinics
Desipramine	(urinary incontinence)
Doxepin (>6 mg)	Darifenacin
Imipramine	Fesoterodine
Nortriptyline	Flavoxate
Paroxetine	Oxybutynin
Protriptyline	Solifenacin
Trimipramine	Tolterodine
	Tropium
Antiemetics	
Prochlorperazine	Antiparkinsonian agents
Promethazine	Benztropine
	Trihexyphenidyl
Antihistamines (first generation)	
Brompheniramine	Antipsychotics
Carbinoxamine	Chlorpromazine
Chlorpheniramine	Clozapine
Clemastine	Loxapine
Cyproheptadine	Olanzapine
Dexbrompheniramine	Perphenazine
Dexchlorpheniramine	Thioridazine
Dimenhydrinate	Trifluoperazine
Diphenhydramine (oral)	
Doxylamine	Antispasmodics
Hydroxyzine	Atropine (excludes ophthalmic)
	Belladonna alkaloids
Meclizine	Scopolamine (excludes ophthalmic)
Clidinium-chlordiazepoxide	
Dicyclomine	Skeletal muscle relaxants
Homatropine (excludes ophthalmic)	
Hyoscyamine	Cyclobenzaprine
Methscopolamine	Orphenadrine
Propantheline	

Main non-drug interventions for dementia



Exercise

Occupational
Therapy

Creative Arts
Therapy

Animal
Assisted
Therapy

Reminiscence

Cognitive
Training

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3 Rules of Agitation Management

Tolerate

- Tolerate as much as possible, the behavior or agitation;

Anticipate

- Anticipate what typically agitates the person;

Don't Agitate

- If you notice that certain things tend to agitate the person, even simple things like reminders, then avoid those things if possible



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Depression

Is it Depression or Dementia?

Symptoms of Depression	Symptoms of Dementia
<ul style="list-style-type: none">•Mental decline is relatively rapid•Knows the correct time, date, and location•Difficulty concentrating•Language and motor skills are slow, but normal•Notices or worries about memory problems	<ul style="list-style-type: none">•Mental decline happens slowly•Confused and disoriented; becomes lost in familiar locations•Difficulty with short-term memory•Writing, speaking, and motor skills are impaired•Doesn't notice memory problems or seem to care

Defining Depression in Older Adults

1. Same criteria as in younger adults, but may not endorse sadness or depressive symptoms; rather, somatic complaints and anxiety
2. SIG E. CAPSS 2 weeks or longer, persistent
 - **S**adness or irritability or dysphoric mood
 - Loss of **I**nterest
 - **G**uilt or feeling like a burden
 - Loss of **E**nergy, fatigue
 - Difficulties **C**oncentrating
 - Loss of **A**ppetite (or increased appetite and weight gain)
 - **P**sychemotor retardation (or agitation)
 - Difficulty **S**leeping or sleeping too much
 - **S**uicidal thoughts or desire to die
3. Must affect social, occupational, or other important areas of functioning

Treatment Considerations

- Older age is a relative risk factor for poor outcomes
- If patient responds, continue Rx for 6 to 12 months
- If two or more episodes, continue on lifelong maintenance treatment
- Even with maintenance treatment, relapse rates are about 50%
- If psychotic symptoms present, need antipsychotic (recommended risperidone 0.25-0.5 mg per day)
- Comorbid depression and significant cognitive impairment particularly resistant to treatment, but antidepressants may slow down progression of CI

Follow **STEPS** When Prescribing

1. Safety (overdose, GI issues, interaction with other meds)
2. Tolerability (especially if patient is fearful and/or focused on side effects)
3. Efficacy (most depressants have similar efficacy)
4. Payment (affordability is critical to compliance)
5. Simplicity (# of times medication taken per day)

Pharmacologic Management

Medication	Starting dose	Therapeutic Dose	MOA	Toxicity concerns
Sertraline	Start 12.5-25 mg	50-100 mg	SSRI	SIADH, OH, falls
Bupropion	150 mg	150-450 daily/BID	SNRI	↑ HR, OH, falls, insomnia, wt loss
Duloxetine	10-40 mg	40-120 mg	SNRI	Fewer cardiac, OH
Venlafaxine	75 mg	150-300 mg	SNRI	↑HR, ↑BP, OH, sweating
Fluoxetine	10 mg	20-80 mg	SSRI	QT prolong*, OH, falls
Mirtazapine	7.5 mg HS	30-45 mg	TCA/TeCA	Lethargy, appetite ↑, agranulocyt
Citalopram	5 mg	20-30 mg	SSRI	QT prolong* (>20), OH, falls
Escitalopram	5 mg	10-30 mg	SSRI	QT prolong* (>10), OH, falls
Paroxetine	10 mg	20-60 mg	SSRI	Anticholinergic , falls, OH
Trazodone	25 mg	25-200 mg	†	Lethargy, OH
Levomilnacipran	20 mg	20-120 mg	SNRI	\$\$\$, OH
Vilazodone	20 mg	20-40 mg	†	\$\$\$, OH
Vortioxetine	10 mg	10-20 mg	†	\$\$\$, OH

†Serotonin Modulator

*>500 ms or increase of 20-60 mg = increased risk of Torsade's de Pointes, 0.8 and 1.2 cases per million person-years

Combinations

1. SSRI + quetiapine (Seroquel) (50 to 200 mg/d)
2. SSRI + olanzapine (Zyprexa) (2.5 to 5.0 mg/d)
3. SSRI + aripiprazole (Abilify) (2.5 to 10.0 mg/d)
4. SSRI + lurasidone (Latuda) (40 to 80 mg/d) (reduced weight gain)
(consider asenaprine [Saphris] (5 to 10 mg bid) (Medicare covered?))
5. SSRI + primavanserin (Nuplazid) (17 to 34 mg/d) (Parkinson's or
Lewy Body NCD) (limited availability; \$1000/30 pills; no MC)
6. SSRI + bupropion (Wellbutrin) (75 to 150 mg/d)
7. SSRI + mirtazapine (Remeron) (7.5 to 15 mg/d)

Important Adverse Drug Reactions

- Serotonin syndrome
 - Flushed skin, muscle twitches/myoclonus, HTN, fever, increased confusion
 - Increased risk with combination of SSRI's, SNRI's, mirtazapine, risperidone
- Hyponatremia (SIADH) – all SSRI's
- Anti-platelet effects, e.g. GI bleeding, bruising, etc. – all SSRIs
- Drug-drug interactions (especially paroxetine, fluoxetine, fluvoxamine)
(ex: donepezil + fluoxetine or paroxetine = cholinergic toxidrome)

3 Reasons Why Rx Is Not Effective

1. Patient does not adhere to the medication regimen
2. Trial with medication at an effective dose is not adequate; trial of 8-12 weeks at therapeutic dose is typical necessary before concluding failure
3. Dose is not high enough; be aware of maximum doses FDA approved, and don't be afraid to reach those limits (but need careful monitoring)

Non-Pharmacologic Treatments

1. Counseling + medications is most effective
2. Cognitive Behavioral Therapy has most evidence of benefit
3. ECT for life-threatening illness or meds + psychotherapy ineffective
4. Repetitive Transcranial Magnetic Stimulation (rTMS) is alternative, but expensive and time-consuming and not as effective as ECT
5. Light Therapy
 - 10,000 LUX delivered for 30 min each day or 5,000-7,500 LUX for 45-60 min/day
 - Distance of no farther than 18 inches from face
 - Seasonal affective disorder, primary indication

ECT Indications

- Fail trials of two antidepressants
- Have intolerance of medications
- Prefer ECT over medications
- Have had previously good response to ECT
- Suffer major depression with psychosis
- Have intense suicidal thoughts or have made a suicide attempt
- Have prominent catatonic symptoms
- Have other factors suggesting a fast response is needed, such as food or fluid refusal

Take Home Points

Not all old age confusion is dementia, consider delirium and depression in differential

Not all dementia is Alzheimer's disease

Always look for the multiple potentially underlying causes of dementia and delirium

Non-pharmacologic prevention and management of delirium and dementia are more effective than medications.

Depression is treatable and often requires combination of Rx and non-Rx approaches