The 3Ds – Delirium, Dementia, and Depression

RAJEEV KUMAR MD CMD FACP

PRESIDENT- POST-ACUTE AND LONG-TERM CARE MEDICAL ASSOCIATION

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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

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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.

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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

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Which D?

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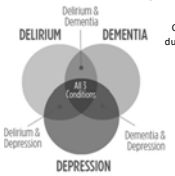
The "Three Ds" Geriatric Syndromes

Acute change in mental status



Cognitive decline due to brain disease

Change in mood with feelings of worthlessness

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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

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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

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Not all old age confusion is dementia

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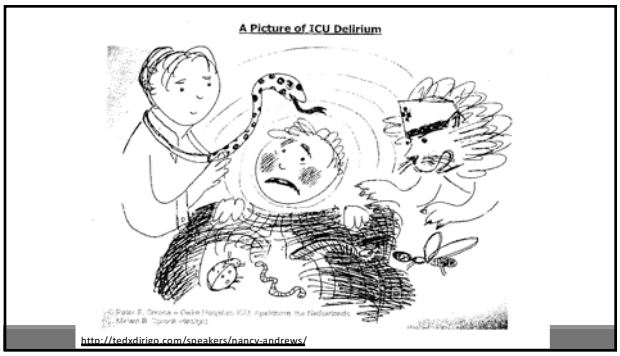

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Delirium

Sudden and frightening onset of
confusion

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Delirium

Difficulty answering questions
Don't make sense
May hallucinate
May be very agitated
Different personality

Hospital care is complex and fragmented.

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DELIRIUM IS…

TRANSIENT, FLUCTUATING, GLOBAL DYSFUNCTION OF COGNITION

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DELIRIUM IS NOT…

DEMENTIA

DEPRESSION

ONLY AGITATION

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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 comative 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 rythm	Increased daytime sleepiness	Prominent disturbances; nightmares and night terrors

Or Mixed!

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

Krzych LJ, et al. Delirium superimposed on dementia in the perioperative period and intensive care. J of Clinical Medicine 2020; 9:1-19

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Is it Delirium or Dementia?

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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.

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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*

Farrell 1995

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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.**

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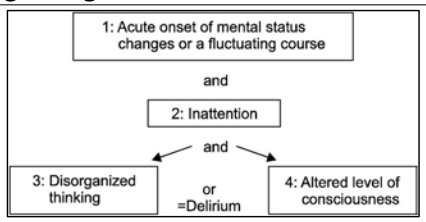
Diagnosing Delirium



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Video example

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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

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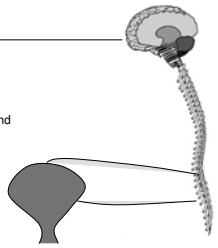
Cystocerebral Syndrome* (Urinary Retention)

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

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

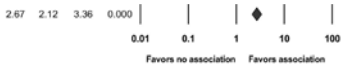

FIGURE 2 Forest plot of the main meta-analysis of 29 studies[20–23,32–56] expressing associations between delirium and UTI in older adults. 95% CI, 95% confidence interval

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.

Krinitski D, et al. J Am Geriatr Soc. 2021;69:3312–3323 23

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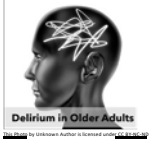
Drugs that can cause an ACUTE CHANGE IN MS

ANTIPARKINSON
Corticosteroid
URIN INCONT
THEOPHLLYINE
EMPTYING DRUGS

CV DRUGS
H2 BLOCKERS
ANTIBIOTICS
NARCOTICS
GERO-PSYCH
ENT

INSOMNIA
NSAIDS

MUSCLE Relaxants
SEIZURE



Flaherty JH. Clinics in Geriatric Medicine, 1998

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Davies N. Nursing Older People. 2021; 33(2):33-41

Managing Delirium

LIMITED DATA IN PALTC

Table 1. Interventions to prevent delirium

Risk factor	Interventions
Cognitive impairment or disorientation	» 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	» 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	» Monitor the person closely for infections and treat these promptly
Limited mobility	» 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	» 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	» 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	» Ensure regular reviews of the person's medications by a pharmacist to modify dosages where necessary

(National Institute for Health and Care Excellence 2018)

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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 KY, 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

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Iglseder B, et al. Wien Med Wochenschr. 2022 Jan 10:1–8.
Hshieh TT, et al. Clinics in Geriatric Medicine 36 (2020) 183–199

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)

Maeda I, et al. J Palliat Med. 2021;24:914–8.

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Dementia

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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

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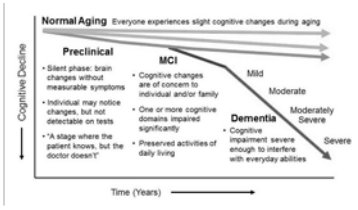
3 stages in the development and progression of Dementia



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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

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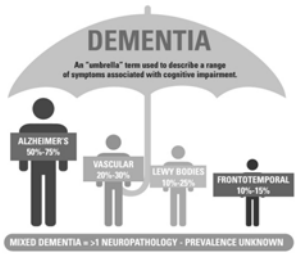
NOT ALL DEMENTIA IS ALZHEIMER'S DISEASE

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



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Common Dementias in Older Persons

Reversible Causes

Alzheimer's disease (hyperamyloidosis)

Hippocampal sclerosis of aging

Primary age-related tauopathy (PART)

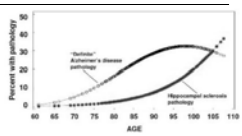
Vascular dementia

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.

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Reversible causes of MCI/Dementia

D rugs
E motional (depression)
M etabolic (hypothyroidism,B12)
E yes and ears (sensory isolation)
N ormal Pressure Hydrocephalus (ataxia, incontinence, and dementia)
T umor or other space-occupying lesion
I nfection (syphilis, chronic infections)
A trial fibrillation/Alcoholism
S leep Apnea

~10 % of all Dementias

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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**

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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

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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

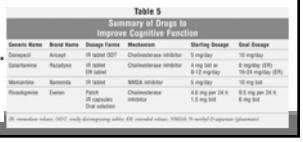
Table 5
Summary of Drugs to Improve Cognitive Function

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

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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

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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

Buckley JS, Salpeter SR. Drugs Aging. 2015 Jun;32(6):453-67.

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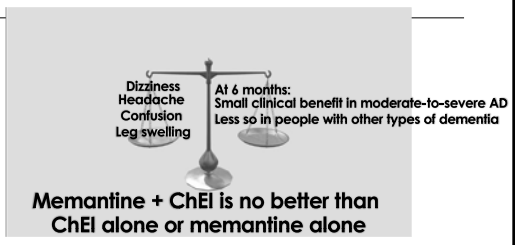
Memantine



McShane R, et al. Cochrane Database Syst Rev. 2019 Mar 20;3(3):CD003154.

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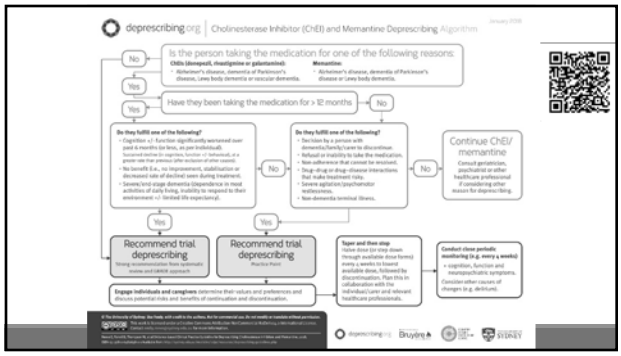

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Drugs That Impair Cognition

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
	Triprolidine
Antidepressants	
Amitriptyline	
Amoxapine	
Clomipramine	Antimuscarinics (urinary incontinence)
Desipramine	Darifenacin
Doxepin (>6 mg)	Fesoterodine
Imipramine	Flavoxate
Nortriptyline	Oxybutynin
Paroxetine	Solifenacin
Protriptyline	Tolterodine
Trimipramine	Trospium
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)
Meclizine	Belladonna alkaloids
Clidinium-chlordiazepoxide	Scopolamine (excludes ophthalmic)
Dicyclomine	
Homatropine (excludes ophthalmic)	Skeletal muscle relaxants
Hyoscyamine	Cyclobenzaprine
Methscopolamine	Orphenadrine
Propantheline	

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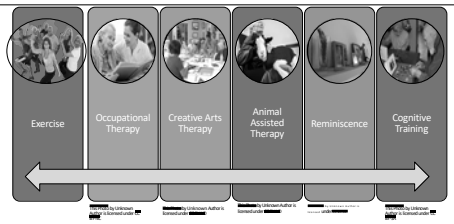
Main non-drug interventions for dementia



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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

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Is it Depression or Dementia?

Symptoms of Depression	Symptoms of Dementia
•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	•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

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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**sychomotor 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

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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

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Follow **STEPS** When Prescribing

1. **S**afety (overdose, GI issues, interaction with other meds)
2. **T**olerability (especially if patient is fearful and/or focused on side effects)
3. **E**fficacy (most depressants have similar efficacy)
4. **P**ayment (affordability is critical to compliance)
5. **S**implicity (# of times medication taken per day)

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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

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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)

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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)

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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)

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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

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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

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