Pharmacology Matters for Alzheimer's Disease and Delirium

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Learning Objectives

State the primary purpose and action of at least one drug that is commonly prescribed/furnished to older adults with Alzheimer’s disease

State the benefits of a thorough assessment for delirium as well as the ramifications of treating with medication before all other interventions have been attempted
Outline

Dementia and delirium defined
Pharmacological treatment of dementia symptoms
• Mild to moderate AD
• Moderate to Severe AD
Risk factors and treatment for delirium
Pharmacological treatment of delirium symptoms
Dementia Defined

Progressive and disabling neurodegenerative disease

*Not* an inherent aspect of aging

Significantly impaired intellectual functioning that interferes with normal activities and relationships

An acquired syndrome of decline in memory and other cognitive functions sufficient to affect daily life in an alert patient

Chertkow (2013); NIH (2015a)
Alzheimer’s Disease (AD) & Related Dementias

Neurodegenerative dementias

• Alzheimer’s disease dementia (#1)
• Lewy body dementia (disease) (#3)
• Frontotemporal dementia
• Semantic dementia

Other dementias

• Vascular (multi-infarct) dementia (#2)
• Other (alcohol, neurosyphilis)

Hugo, J. & Gangull, M. (2014)
Alzheimer’s Disease

Full etiology is not known!

What we think we know about the pathophysiology

- deficits of acetylcholine
- $\beta$-amyloid deposits
- $\tau$-protein phosphorylation
- oxidative stress
- neuroinflammation
- and, more

Latest thinking is that AD is a complex multifactorial disease process!

Unzeta (2016)
Pharmacology of Drugs Commonly Given to Persons with AD

- Two major categories of drugs
  - Cholinesterase inhibitors
    - Prevents break down of acetylcholine
  - N-methyl D-asparate (NMDA) antagonist
    - Blocks toxic effects of excessive glutamate

- Prescribing guidelines, but “Treatment should be individualized” Cummings et al (2015)

- Prescribed for symptoms
  - “These drugs provide symptomatic relief but poorly affect the progression of the disease.” Salomone, et al (2012)

NIH (2015a)
So, what is meant by symptoms?

Behavioral and psychological symptoms

- Restlessness
- Aggression
- Sleep disturbances
- Hallucinations
- Delusions
- Apathy
Cholinesterase inhibitors (prevent the breakdown of acetylcholine)

- **Galantamine (Raxadyne)**
  - 8mg to 16mg to 24mg per day in divided doses (at min of 4 wk intervals)

- **Rivastigmine (Exelon)**
  - Capsule: 3mg to 6mg to 9mg to 12mg per day in divided doses (at min of 2 wk intervals)
  - Patch: 4.6mg to 9.5mg to 13.3mg per day (at min of 4 wk intervals)

- **Donopezil (Aricept)**
  - 5mg to 10mg to 23mg per day (varying intervals)

NIH (2015a)
Mild to Moderate AD

Cholinesterase inhibitors (prevent the break down of acetylcholine)

- Galantamine (Raxadyne)
- Rivastigmine (Exelon)
- Donopezil (Aricept)

Side effects include nausea, vomiting, diarrhea, muscle weakness/cramps, wt loss

“These drugs may help delay or prevent symptoms from becoming worse for a limited time and may help control some behavioral symptoms.” (NIH, 2015b)
Moderate to Severe AD

N-methyl D-aspartate (NMDA) antagonist (blocks toxic effects of excessive glutamate)

- Memantine (Namenda): 5mg to 10mg to 15mg to 20mg per day in divided doses (at min of 1 wk intervals)
  - Side effects: headache, dizziness, diarrhea, constipation, confusion

- Memantine hydrochloride extended-release and donepezil hydrochloride (Namzaric)
  - combo of memantine 28mg & donepezil 10mg per day (14mg + 10mg for severe renal failure)
  - Side effects: headache, nausea, vomiting, dizziness, diarrhea

NIH (2015b)
Dementia Summary

There is no cure for the neurodegenerative dementias, including Alzheimer’s disease.

Common uses for cholinesterase inhibitors & NMDA antagonist are to treat behavioral and psychological symptoms in AD.

Drugs used for symptoms are typically effective for 6-12 months.
Now, let’s look at delirium
Delirium Defined

Delirium is a common, life threatening and preventable geriatric syndrome characterized by:

- Fluctuating mental status
- Inattention
- Disorganized thinking
- Altered level of consciousness

- “Delirium is an acute decline in cognitive function and attention and represents brain failure.”
  - (AGS Expert Panel, 2015)
Risk Factors for Delirium

- Preexisting cognitive impairment
- Age
- Infection
- Acute systemic illnesses/comorbid conditions
- Severity of illness
- Polypharmacy/high risk medication use
- Diminished ADLs
- Immobility
- Sensory impairment
- Urea and electrolyte imbalance
- Malnutrition

(Ahmed, Leurent, & Sampson, 2014; Inouye et al., 1990; Boltz, Capezuti, Fulmer & Zwicker, 2016)
Outcomes of Delirium

Increased mortality rate
Increased hospital stay
Transfer to long term care facilities
Depression
Decreased functional and cognitive status

22% to 89% of older hospitalized adults with dementia experience delirium, are at increased risk of developing delirium and have worse outcomes

(AGS, 2015; Inouye, 1998)
Multicomponent nonpharmacological interventions

- Walking/mobility
- No restraints
- Orientation
- Encourage regular habits
- Adequate oxygenation
- Fluids and nutrition
- Ongoing education to health care providers
- Medical evaluation to manage underlying medical contributors to delirium

(AGS, 2015)
Multicomponent delirium prevention protocol: targets 6 risk factors
Cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration

- Daily visits
- Therapeutic activities
- Assistance with feeding, hydration, sleep, and vision/hearing impairment

(Inouye, Bogardus, Baker, Leo-Summers & Cooney, 2000)
Pain management (non opioid medications)
High risk medication discontinued/avoided

***”Prophylactic administration of newly prescribed cholinesterase inhibitors are not effective in reducing postoperative delirium and may cause harm (including mortality).” (AGS, 2015)

***Benzodiazepines should not be used as first-line treatment of agitation associated with delirium

Antipsychotics and benzodiazepines should be avoided for treatment of hypoactive delirium

(McCormick, 2015; AGS, 2015)
Anticholinergics, sedative hypnotics, and meperidine increase the risk of postoperative delirium in older adults

- Diphenhydramine increases the odds ratio of developing delirium to 2.3
- Benzodiazepines had an increased odds ratio of 3.0.
- Meperidine associated with delirium with an odds ratio of 2.7

***avoidance of agents prone to increasing the risk or severity of delirium

(AGS, 2015)
Pharmacological Treatment

No benzodiazepines for first-line treatment of agitated post operative delirious patient except when indicated for alcohol or benzodiazepine withdrawal.

Lowest effective dose and shortest possible duration for severe agitation only if behavioral measures have failed.

There is no evidence of benefit from treatment of antipsychotics in patients without agitation.

No evidence supports use of benzodiazepines in treatment of delirium.

(AGS expert panel, 2015)
Antipsychotics only when patient is “severely agitated or distressed, threatening substantial harm to self or others and used only if behavioral interventions have failed or are not possible”.

Ongoing use evaluated daily

Do not prescribe antipsychotics or benzodiazepine meds for those patients who are not agitated.

Lorazepam administration is an important and potentially modifiable risk factor for transitioning into delirium.

(Pandharipande, et al. 2006; AGS, 2015)
Antipsychotics

National Institute for Health and Care Excellence (NICE)

• Evidence for pharmacological interventions is limited
• Use antipsychotic drugs with caution or not at all for people with dementia with Lewy bodies
• If a person with delirium is distressed or risk to themselves or others, consider giving short-term haloperidol or olanzapine.

(NICE, 2010)
Current Evidence

There is no current evidence that supports the routine use of benzodiazepines in the treatment of delirium. Much evidence benzodiazepines promote delirium. Benzodiazepines remain the recommended treatment for alcohol withdrawal.
Future Research: AGS/NIA Bedside to Bench Conference

Delirium: interface with other geriatric syndromes
Stress physiology, immunology and delirium
Delirium biomarkers: Associations with dementia
Delirium and Cognitive Sequelae
Delirium Interventions
Priorities for Research:
• Delirium and Geriatric Syndromes
• Delirium Phenomenology (hypoactive, hyperactive, superimposed on dementia)
• Delirium Pathophysiology and Basic Mechanisms
• Biomarkers of delirium
• Measurement and Quality Control in delirium research

(AGS/NIA, 2015)
Summary

There is no silver bullet...
Delirium is a common, life threatening and preventable geriatric syndrome
Multicomponent nonpharmacological interventions
Lowest effect dose and shortest possible duration for severe agitation only if behavioral measures have failed
Pharmacological interventions only after a thorough assessment and minimization of risk factors while addressing illness/comorbid conditions.


References


