Managing Major Geriatric Syndromes - Fact, Fiction, Updates and Clinical Pearls

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Financial Disclosure and Resolution

I have no relevant financial relationships with ineligible companies to disclose.

Data and recommendations presented may include information not included in product labelling.

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Learning Objectives

At the completion of this activity, pharmacists will be able to:

- Compare the pharmacologic activity and potential adverse effects of medications used to manage dementia
- Predict the potential benefits and risks associated with the use of medications commonly used to treat urinary incontinence
- Describe the known benefit of medications and nutritional supplements used to reduce the risk of recurrent urinary tract infections
- Examine the potential benefits and risks associated with therapies for managing the behavioral and psychiatric symptoms of dementia
- Summarize the potential benefits and risks associated with medications used to manage weight loss in older individuals

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General Considerations

- Geriatric Syndromes: "multifactorial health conditions that occur when the accumulated effects of impairment in multiple systems render an older person vulnerable to situational challenges. A defining feature of geriatric syndromes is that multiple factors contribute to their etiology." (JAGS 2007)

JAGS 2007, 55:780-791

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General Considerations

- Clinical conditions in older persons that do not fit into discrete disease categories
- Highly prevalent, multifactorial and associated with substantial morbidity and poor outcomes
- Four shared risk factors – older age, baseline cognitive impairment, baseline functional impairment, and impaired mobility
- Common geriatric syndromes – pressure wounds (ulcers), incontinence, falls, functional decline, weight loss, and delirium

JAGS 2007, 55:780-791

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Conditions Commonly Associated with "Geriatric Syndromes"

- Incontinence
- Falls
- Functional decline
- Pressure wounds (decubitus ulcers)
- Dementia
- Delirium (altered mental status – AMS)
- Weight loss
- Osteoporosis
- Polypharmacy

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Special Considerations

- Multiple risk factors and multiple organ systems are often involved
- Strategies to identify underlying cause(s) often ineffective, burdensome, dangerous and costly
- Therapeutic management of clinical manifestations helpful even in the absence of a firm diagnosis

JAGS 2007, 55:780-791

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Updates in Dementia Therapy

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Section Objectives

- Recommend first line treatment options for the various types of dementia
- Discuss current concerns associated with the use of beta-amyloid modulating therapies recently approved by the FDA
- Suggest contraindications to use of typical therapies used to treat dementia
- Compare potential benefit and risk associated to common agents used to manage behaviorial and psychiatric symptoms of dementia (BPSD)
- Suggest situations where use of psychotropic medications may be associated with significant risk in elderly individuals with dementia

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Delirium, Dementia & AMI

- Age-Associated Memory Impairment
  - Normal aging (slip of tongue, word searching)
  - Should not affect functioning
- Dementia
  - Chronic cognitive deterioration
  - Progressive
- Delirium
  - Acute confusional state
  - Altered consciousness
  - Reversible

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Differentiating Dementias

- Typical Aging – Age Associated Cognitive Decline (AACI)
  - Recent memory for important events intact
  - Occasional difficulties with word finding
  - ADLs intact; normal performance on MSE
- Mild Cognitive Impairment - MCI
  - Memory complaints only
  - ADLs intact; minimal changes in other areas
  - High risk of progression to dementia
    - 50% progress to dementia within 5 years

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.
JAMA.2019;322(16):1589-1599.doi:10.1001/jama.2019.4782

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Differentiating Dementias

- Alzheimer's Disease (AD)
  - Most common form of dementia
  - Slow onset and continued cognitive decline
  - Symptoms
    - Short-term memory impairment
    - Language difficulties
    - Loss of executive function
      - Abstract thinking, reasoning, planning
    - Mood and personality changes
    - Psychiatric and behavioral symptoms (late stages)
    - Extrapyramidal features, e.g. bradykinesias (late stages)

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.

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Differentiating Dementias

- Vascular Dementia (VaD)
  - New term: VCID – vascular contribution to cognitive impairment
  - Past term: Vascular Cognitive Impairment (VCI) or multi-infarct dementia
  - Patient aware of deficits
  - Focal neurologic signs
  - Temporal relationship with "event" or vascular pathology and risks (HTN, DM, Smoking)
  - Abrupt deterioration with stepwise progression
  - Executive dysfunction, depression, apathy, behavioral changes more prevalent than in AD

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.

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Differentiating Dementias

- Lewy Body Dementia (DLB)
  - Intracellular inclusions in substantia nigra (dopamine and Ach deficits)
  - Beta-amyloid/senile plaques (but not neurofibrillary tangles)
  - Dementia with prominent extrapyramidal motor symptoms early in disease (PD with dementia)
    - Rapid eye movement may be noted for years prior to cognitive impairment
    - Antipsychotics worsen symptoms or cause life-threatening dyskinesias and neuromalignant syndrome
  - Fluctuating mental and physical status
    - Hallucinations and "parkinsonism"
    - Apathy, depression, visual-spatial impairment, verbal-blocking common

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.

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Differentiating Dementias

- Frontotemporal Dementia
  - Prominent personality changes with disinhibition and apathy common
  - Deterioration of social skills and reduced verbal output with spared drawing and calculation abilities
  - Variable effect on memory
  - Typical therapies (AChIs) may worsen symptoms

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.

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Etiology of Alzheimer's Disease

- Early Onset (5%)
  - Amyloid Precursor Protein
  - Presenilin 1
  - Presenilin 2
- Late Onset
  - Apo E4 genotype
- Environmental factors

- Neuropathologic changes
  - Cortical and limbic atrophy
  - Neurotransmitter degeneration (↓Ach)
  - B-amyloid neuritic plaques
  - Neuofibrillary tangles (phosphorylated tau protein)

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Clinical Features

- Deterioration in function
  - Decreased basic ADLs
    - Bathing, toileting, dressing, feeding oneself
  - Decreased IADLs
    - Managing finances, shopping, cooking, cleaning, maintaining independent lifestyle
- Behavioral disturbances
- Cognitive impairment
- Decline in global function

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Delirium

- Present in up to 50% of hospitalized elderly patients
- 8-17% on admission; 40% of NH residents
- Increased risk of negative outcomes:
  - Increased length of stay
  - Functional decline
  - Nursing home/rehab center placement
  - Mortality
  - Increased costs (direct and indirect)

Risk Factors:
- Dementia or other cognitive impairment
- Functional impairment
- Sensory impairment
- Substance abuse
- Advanced age
- Comorbidity
- Stroke, depression, medical disorders, infection

Inouye KS, et al. Lancet 2014;383:911-22.

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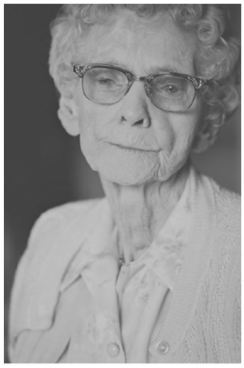
Delirium Summary

- Acute, fluctuating cognitive impairment
- Sign of an underlying medical condition
  - Primary treatment to address this condition
- Symptomatic treatments can help
- Environmental management can help



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Drugs That May Induce Delirium

High Risk	Moderate Risk	Lower Risk
Antidepressants (esp. tricyclics)	Alpha-blockers	ACEIs
Antipsychotics	Antiarrhythmics	Anti-Asthmatics (theophyline)
Dopaminergic Drugs	Beta-blockers	Antibacterials
Opioid Narcotics	Digoxin	Anticonvulsants
Benzodiazepines	NSAIDs	Calcium Channel Blockers
Corticosteroids	Postganglionic Blockers	Diuretics
Lithium		H_2 Antagonists
Alcohol Withdrawal		

Borovicka and Fuller. Delirium. In: Tisdale and Miller eds. Drug-Induced Diseases: Prevention, Detection, and Management. 2005. American Society of Health-System Pharmacists. Bethesda, MD.

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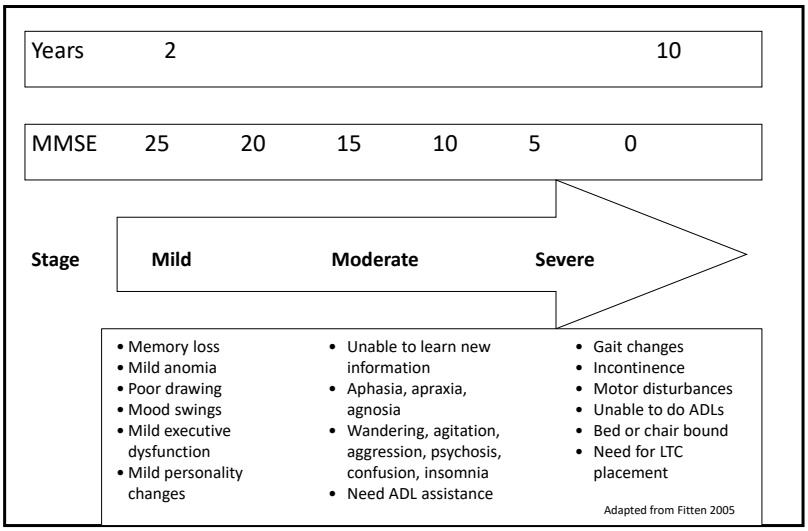
Progression of Dementia



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Key Issues in Dementia Treatment

- Eliminate or minimize drug-related adverse reactions
- Address concurrent diseases that resemble or complicate treatment
- Improve cognitive performance and treat related symptoms such as psychiatric and behavioral disturbances

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Treatment of Dementia

- Relies on early recognition and accurate diagnosis
- Goals
  - Improving cognition
  - Possibly delaying progression
  - Managing psychiatric and behavioral manifestations
- Patient and family support

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Treatment Options

- AChE Inhibitors – use throughout illness; indicated in mild to severe disease
- NMDA Inhibitors – indicated in moderate to severe disease
- Anti-amyloid therapies – aducanumab, others
- Therapy for noncognitive symptoms
  - Antipsychotics
  - Mood stabilizers
  - Antidepressants
  - Sedatives/hypnotics

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Cholinesterase Inhibitors

- Mechanism: reduce hydrolysis of acetylcholine after release by presynaptic neurons – increases Ach
- Class ADRs –
  - GI – Nausea, vomiting, diarrhea, anorexia
  - CNS – sedation or insomnia
  - CV – bradycardia (similar to vagal effect)
- Examples:
  - Donepezil
  - Rivastigmine
  - Galantamine

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Cholinesterase Inhibitors

- Donepezil
  - Lowest rates of nausea, vomiting and anorexia; increased with 23 mg dose
  - Long half-life favors once daily dosing; compliance
  - Approved for mild, moderate and severe dementia
  - Available in combination with memantine
  - Recent approval of a weekly topical patch
- Rivastigmine (also inhibits butyrylcholinesterase)
  - Available in transdermal form
    - Reduces nausea and approved for mild, moderate and severe dementia
  - Oral form approved for mild, moderate dementia
  - Only ChEI approved for Parkinson's dementia
- Galantamine
  - Approved for mild-moderate dementia only
  - Greatest risk of CYP interactions
  - IR form requires BID dosing

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Measuring Treatment Effectiveness

- Alzheimer Disease Assessment Scale: Cognitive Subscale (ADAS-Cog)
- Clinician Interview-based Impression of Change scale and Clinical Global Impression of Change scale (CIBIC)
- Folstein Mini Mental Status Examination (MMSE)

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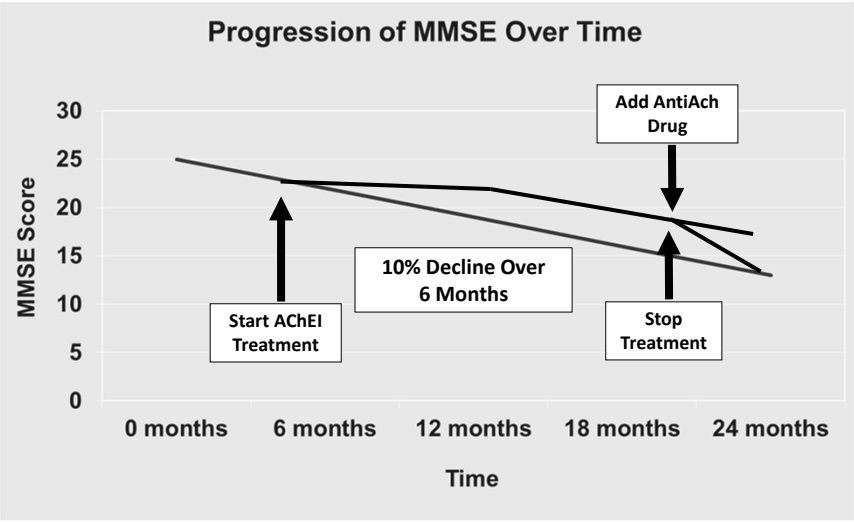
Models of Treatment Response



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Cholinesterase Inhibitor General Statements

- "Palliative treatments"
- Small but measurable benefits
  - Symptom progression delayed by ~ 4 to 9 months in most studies
- Adverse effects vary considerably
- Longer half-life benefits noncompliant patients
- Efficacy established in mild to moderate disease
- Discontinued due to ADRS or lack of efficacy

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N-Methyl-D-Aspartate Antagonists (NMDA)

- Memantidine (Namenda®) –
  - Characteristics
  - Indication – moderate to severe AD
  - Dosing
    - Initial dose 5mg once daily. Increase dose in 5mg increments at weekly intervals.
    - IR: Target dose of 20 mg daily
    - ER Doses available: 7mg, 14mg, 21mg, 28mg
    - Available in combination with donepezil – lower ChEI-adverse effects (less anorexia, n/v)
    - Reduce dose with moderate renal impairment.
  - ADRs
    - Headache, dizziness, drowsiness/confusion, agitation/anxiety, increased BP, seizure risk(?)
- Memantine + Donepezil (Namzaric®)
  - 7-10, 14-10, 21-10, 28-10

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Aducanumab (Aduhelm)

- Recombinant human immunoglobulin G1 (IgG1) monoclonal antibody
- Designed to promote clearance of cerebral amyloid aggregates and insoluble forms of Aβ
- Provisional approval by FDA in June 2021
- Considerable controversy – limited efficacy and significant
- Approval "based on reduction in Aβ plaques observed in patients treated with Aduhelm" rather than compelling evidence of a change in clinical measures"

Day GS, Scarmeas N, Dubinsky R, et. al. Aducanumab Use in Symptomatic Alzheimer Disease Evidence in Focus 2022:98(15);619-31.

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Aducanumab Summary

- Expected benefit
  - Reduces cerebral amyloid plaques measured by amyloid PET.
  - Efficacy evaluated in three separate studies (3,482 patients)
  - Treated patients demonstrated significant dose-and time-dependent reduction of amyloid beta plaque (surrogate marker for AD progression)
  - Unknown if improvements in function, cognition, quality of life, maintenance of independence, or survival.
- Risks
  - Amyloid-related imaging abnormalities with edema/effusion (ARIA-E) in 41% of patients
  - 25% with ARIA had symptoms (approximately 10% overall); most resolved with drug cessation
  - Other common risks - headache, confusion, dizziness, nausea infusion reactions
  - AE-associated decreases in cognition, quality of life, independence, and survival possible

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Aducanumab Summary

- Commitment/burden
  - Must see a specialist to be assessed for treatment
  - Requires infusions every 4 weeks at specialized centers
  - Confirmation of elevated amyloid via a specialized brain scan (amyloid PET scan, not covered by Medicare or most insurers) or lumbar puncture with CSF testing (currently covered)
  - At least 16 days/year to complete evaluations, investigations, and infusions
- Cost
  - Brain MRIs needed - prior to initiation and then at least twice yearly
  - Monthly IV dosing with escalating doses – maintenance dose 10 mg/kg costs approximately $2400 per dose (SQ dosing under investigation)
  - Estimated drug cost = $28,000/year or more
  - Additional costs - pretreatment evaluations, follow-up visits, investigations, and drug infusion
  - Suspected AEs may require substantially greater commitment.

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Lecanemab (LEQEMBI™)

- Adverse Effects:
  - Amyloid Related Imaging Abnormalities (ARIA) - temporary swelling in the brain – identified by MRI and associated symptoms (swelling in areas of the brain, with or without small spots of bleeding in or on the surface of the brain)
  - Infusion-related reactions
  - Headache
- Modest beneficial effects:
  - Measurable reduction in amyloid beta levels
- Controversial Use – Major professional groups recommend ‘Do not use’ anti-amyloid monoclonal antibody therapies

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General Statements on Dementia Therapies

- Modest evidence of ChEIs in mild to moderate AD and memantine for moderate to severe AD
- Higher doses of donepezil not clinically superior
- Higher doses of transdermal rivastigmine may show greater benefit
- Recent trials with memantine in mild-moderate AD not clinically beneficial
- Newer trials show slight or unclear benefit when memantine added to ChEIs
- Updated evidence on safety of ChEIs
  - Anorexia, weight loss, falls, hip fractures, syncope, bradycardia, and increase pacemakers
- Benefit/impact of monoclonal treatments unknown

Rabins PV, et al. American Psychiatric Association 2014
http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf

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Treatment Decisions in Dementia

- When to initiate treatment?
- When to combine therapies?
- When to add and what adjunct therapies to add?
- When to stop cognitive therapies?
- When to withdraw other therapies?

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Discontinuing Cholinesterase Inhibitors in Patients with Dementia

- Stopping therapy recommended:
  - Non-adherence
  - Continued deterioration
  - Terminally ill or serious comorbidity
  - Patient or caregiver choice
- Domino Trial (2012):
  295 patients with mod/severe AD on donepezil ≥ 3 months (MMSE and Bristol ADL scale)
  - Continued donepezil → ~ 32% less decline
  - Switch to memantine → less pronounced decline (~ 20% less)
  - Addition of memantine → no additional benefit
  - Discontinuation of donepezil → worsening condition

Winslow BT, et al. Am Fam Physic 2011;83(12):1403-12.
Howard R et al, NEJM 2012; 366(10):893-903

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Behavioral and Psychological Symptoms of Dementia (BPSD)

- Behavioral disturbances are common
  - ≥ 80% of patients with AD will experience agitation
  - ~ 40% of patients with AD experience aggression
- Assessment requires going back to the ABC's
  - Antecedents–
    - What triggered the behavior?
    - Assess for pain or other modifiable contributors to symptoms
  - Behavior–
    - What type of behavior?
    - Is it a target for intervention?
  - Consequences–
    - To whom? The patient or others?
    - Serious episodes may result in discharge to another level of care

Reus VI, et al. Am J Psychiatry 2016;173:543

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Neuropsychiatric Symptoms

- Hallucinations
  - Auditory/Visual
- Delusions
  - Persecutory
  - Theft
  - Infidelity
  - Capgras syndrome
- Anxiety
  - Agitation/Combative
  - Restlessness, others
- Psychomotor activity
  - Wandering/Pacing
  - Purposeless activity
- Personality
  - Disengagement
  - Disinhibition
  - Emotional blunting
- Mood Changes
  - Depressive symptoms
  - Elevated mood
  - Mood lability
- Miscellaneous
  - Appetite changes
  - Sleep Disturbances
  - Changes in sexual activity

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BPSD Clusters, Symptoms & Consequences

Cluster	Symptoms	Consequences
Depression	**Sadness, crying, hopelessness, guilt, anxiety**	**Poor self care Weight loss**
Apathy	**Withdrawal, lack of pleasure**	**Isolation, reduced self-care & hygiene**
Aggression	**Resistance to care; physical or verbal**	**Altercations Injuries**
Psychomotor agitation	**Wandering, pacing, sleep disturbances, repetitive actions, intrusiveness**	**Escaping (exiting/eloping) Altercations**
Psychosis	**Delusions, hallucinations**	**Isolation Refusal of care**

Reus VI, et al. Am J Psychiatry 2016;173:543

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Psychotic Symptoms in Elders

- Symptoms of psychosis common
  - Community-dwelling elders – 0.2% to 4.75%
  - LTC residents – 65% or higher
- Antipsychotic prescribing common
  - Often used for BPSD
  - Very old (>85) very likely to be prescribed antipsychotics (20%), benzodiazepines, and antidepressants

Chahine LM, et al. The elderly safety imperative and antipsychotic usage. Harv Rev Psychiatry 2010;18:158-172.

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Concerns with Use of Antipsychotics in Dementia

- Typical adverse effects
  - Somnolence and altered cognition
  - Falls
  - Anticholinergic effects
  - Hypotension
  - Dystonias
- Serious adverse effects
  - Sudden death, stroke
  - Pneumonia and hospitalizations
  - Parkinsonism and tardive dyskinesia
  - Neuroleptic malignant syndrome and serotonin syndrome
- Other effects
  - Weight gain, diabetes, metabolic syndrome
  - Bone marrow suppression
  - Infections
  - Seizures
  - Hormonal disturbances
  - Altered thermoregulation
  - Cataracts
  - Sexual dysfunction and priapism

Black Box Warning

Chahine LM, et al. The elderly safety imperative and antipsychotic usage. Harv Rev Psychiatry 2010;18:158-172.

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Fall Risk with Antipsychotic Use in the Elderly

- FDA Labeling Update in February 2017; Warnings section
- Somnolence, postural hypotension, motor or sensory instability, may lead to falls or injury (including fracture)
- Risk of orthostasis mediated by α1 antagonism

Low	Moderate	High
Aripiprazole Ziprasidone Haloperidol	Risperidone Quetiapine	Clozapine Iloperidone Chlorpromazine

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Antipsychotic Risks in the Elderly

Adverse Effects	FGAs - Greatest Risk	SGAs - Greatest Risk
Sedation	Low potency – chlorpromazine	Quetiapine
Parkinsonism	High potency – haloperidol, fluphenazine	Risperidone
Akathisia	High potency	Aripiprazole, lurasidone
Metabolic syndrome	Low potency	Olanzapine, clozapine
Orthostasis	Low potency	Quetiapine, clozapine
QTc prolongation	Thioridazine, pimozide, haloperidol IV	Ziprasidone, quetiapine, clozapine
Severe neutropenia		Clozapine

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Antipsychotic Use in the Elderly APA Recommendations

- Benefits should outweigh risks
- Low initial dose and titrate to lowest effective dose
- Gradual Dose Reduction (GDR)
  - After 4 weeks if no improvement
  - After 4 months with response
  - Recurrence of symptoms with GDR indicates continued treatment warranted
- Monitor for relapse for at least 4 months after discontinuation

Reus VI, et al. Am J Psychiatry 2016;173:543-6.

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Antipsychotic Use in Elders with Movement Disorders

- Parkinson's Disease, Parkinson's Disease Dementia, or Lewy-Body Dementia
- Increased risk of extrapyramidal symptoms (EPS) with antipsychotics
- Avoid high-potency antipsychotics – esp. haloperidol
- Consider use of quetiapine or clozapine (non-FDA use)
  - Clozapine: monitor Absolute Neutrophil Count (ANC) due to risk of neutropenia
- Pimavanserin (Nuplazid)
  - FDA approved for Parkinson's disease psychosis
  - Not approved for psychosis in dementia

Panchal SC, et al. Curr Psychiatry Reports 2018;20:3; Bozymski KM, et al. Ann Pharmacother2017;51:479-87. www.clozapinerems.com

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Dextromethorphan & Quinidine (Nuedexta)

- NMDA receptor antagonist (dextromethorphan) plus enzymatic inhibitor (quinidine) indicated for pseudobulbar affect
- Sometimes used 'off label' for agitation/aggression in Alzheimer Disease and other dementias
- Considered 'potentially inappropriate' in AGS Beers Criteria – use not recommended

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Dementia Clinical Pearls for BPSD

- Assess for pain, infection - rule out delirium
- Remove delirium-associated medications
- Employ behavioral interventions
- Educate caregivers and staff
- Add cholinesterase inhibitor
- Consider antidepressant
- If no other options remain…consider an antipsychotic
- Discuss benefit vs. risk and reevaluate continued use and attempt dosage reduction and deprescribe

DeMers S, et al. Med Clin NA. 2014; 98:1145–1168. Reus VI, et al. Am J Psychiatry 2016;173:543-6.
Sink K. et al. JAMA 2005;293(5):596–608.

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Updates in Therapy for Urinary Incontinence

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Section Objectives

- List causes of urinary incontinence
- Discuss principles to guide therapy of urinary incontinence
- List the advantages and disadvantages of the agents available to treat stress incontinence and urge incontinence in the elderly
- Discuss the use of agents to treat urinary incontinence due to benign prostatic hyperplasia
- Recommend treatment for an older person dependent upon the type of urinary incontinence and the relative efficacy and toxicity of available agents
- Suggest situations where incontinence medications may be associated with significant risk in elderly individuals

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Urinary Incontinence (UI)

- Loss of bladder control —a common and often embarrassing problem
- Symptoms and severity vary
  - Occasional leaking urine with coughing or sneezing
  - Urge to urinate that's so sudden and strong you don't get to a toilet in time
  - Sudden emptying of bladder with little or no warning

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Types of Urinary Incontinence

- Urge incontinence (OAB) –
  - Sudden, intense urge to urinate followed by involuntary loss of urine.
  - Increased need to urinate often, including throughout the night
  - Sometimes caused by a identifiable condition - infection, neurologic disorder or diabetes
- Stress incontinence –
  - Urine leaks with increased abdominal pressure on your bladder (coughing, sneezing, laughing, exercising or lifting something heavy)
  - Often results from pregnancy or other alteration to pelvic 'floor'

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Types of Urinary Incontinence

- Overflow incontinence –
  - Frequent or constant dribbling of urine due to a bladder that doesn't empty completely
  - May cause sudden emptying of large amounts of urine
- Functional incontinence –
  - Influenced by physical barriers or mental issues interfering with routine and regular use of restroom facilities
  - Causes - poor vision, psychological issues, cognitive issues, neurological or muscular limitations (stroke, Parkinson disease, arthritis, etc.) or environmental barriers to using the restroom (lack of assistance, non ADA-compliant facilities)

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Epidemiology

- Urinary leakage in 30% to 40% of older individuals living in their own homes or apartments in the U.S. (2014 data)
- Moderate or severe urinary incontinence requiring medical treatment in 24% older adults in the U.S.
- Costly to individuals, health care systems and long term care industry (direct cost of bladder control products)
- Incontinence (with or without injury) - a leading cause of admission to assisted living and nursing care facilities
  - > 50% of nursing facility admissions related to incontinence

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Epidemiology

- Women > 60 years twice as likely as men to experience incontinence
- One in three women > 60 years have bladder control problems.
- Weakening of pelvic floor muscles from pregnancy commonly associated with increasing risk of incontinence

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Medication Causes/Contributors to Urinary Incontinence

- Urgency, frequency, polyuria
  - Acetylcholinesterase inhibitors, diuretics, lithium, caffeine, alcohol
- Urinary retention
  - Alpha 1 receptor agonists (especially in men)
    - phenylephrine, phenylpropanolamine, clonidine, guanfacine
  - Anticholinergic drugs
    - antihistamines, antiparkinsonian agents, antidepressants, antipsychotics
  - Beta-agonists
  - Opioids and other sedatives
- Urethral underactivity
  - Alpha 1 receptor antagonists (in women – carvedolol, labetolol , mirtazepine, tarazosin, doxazosin) ,
- ACE inhibitors (induce cough)

Adapted from Lackner TE, Clinical Consult, 2001;16:(S2) 1-15

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Treatment of Incontinence

- Non-Drug therapies - for both urge incontinence and stress incontinence
  - Bladder training
  - Pelvic floor muscle training
- Medical devices:
  - Indwelling urinary catheters are not recommended
  - External 'collection' devices and supplies
    - Adult diapers and pads
    - 'Texas catheters'
    - Nighttime leak collection and removal devices

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Pharmacotherapy of Urge Incontinence (UI)

- Start medications at the lowest possible dose in the elderly
  - Minimize common side effects leading to premature discontinuance of the medication
  - Early adverse effects may decrease or disappear
- Allow a sufficient time assess efficacy
  - Full response often delayed for weeks – oxybutynin(4), tolterodine(10), estrogen(12) and finasteride(16)
- Successful treatment reduces overall cost of UI
- Concomitant behavioral therapy (bladder training) may enhance drug response while cognitive decline may blunt impact

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Pharmacotherapy for Urge Incontinence

- Anticholinergics – 6 different agents now available
- Oxybutynin
  - Immediate Release (Ditropan® and generics) –
  - Extended Release (Ditropan XL ® and generics) –
  - Transdermal patch – twice weekly (Alleged decreased anticholinergic effects) – Prev. RX now OTC patch applied every 4 days
  - Gel (Gelnique ®) – daily application (Alleged decreased anticholinergic effects)
  - Change doses no more frequently than once per month
- Tolterodine
  - Immediate Release (Detrol ® and generics) –
  - Extended Release (Detrol LA ® and generics) –
  - Change dose no more frequently than once per month

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Anticholinergics (continued)

- Trospium chloride (Sanctura ®) and generics–
  - Dose typically BID – reduce to once daily with renal insufficiency/elderly
  - Trospium chloride ER 60 mg
- Solifenacin succinate (VESIcare®) – once daily dosing
  - Drug interaction with potent 3A4 inhibitors (clarithromycin, ketoconazole, ritinovir)
- Darifenacin hydrobromide (Enablex®) and generic – once daily dosing
  - Drug interactions with potent 3A4 inhibitors
- Fesoterodine (Toviaz ®)
- Newer agents target M3 receptor (fewer systemic anticholinergic effects) but clinical effects and toxicities similar to tolterodine and oxybuynin

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Efficacy of Anticholinergics in Urge Incontinence

- MOA: Muscarinic receptor antagonists act on the smooth muscle of the bladder to decrease bladder contractility and increase bladder capacity
- Reduce urge incontinence by 15 to 60% (Oxybutynin and tolterodine)
- Immediate release oxybutynin superior to immediate release tolterodine
  - Extended release formulations reported equally effective
- Overall effect modest at best

(Medical Letter)

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Toxicity of Anticholinergics in Urge Incontinence

- Drop out rate for oxybutynin IR = 20%
  - Severe dry mouth (xerostomia) causing taste disturbance, anorexia, difficulty chewing, esophogeal dysmotility
- Drop out rates for oxybutynin XL and the tolterodine compounds <10%
  - Dry mouth most common complaint

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Toxicity of Anticholinergics in Urge Incontinence

- Other side anticholinergic effects include: dry eyes, blurred vision, constipation, reflux, confusion and tachycardia
  - Oxybutynin – most frequent anticholinergic effects – decreasing use and elimination from some formularies (IR formulation on BEERs List)
- Tolterodine – fewer troublesome CNS effects reported than with oxybutynin - less likely to cross the blood-brain barrier

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Comparative Costs (2022 costs*)

- Oxybutynin IR (generic) - BID dosing - $0.50 to $1.50 daily
- Oxbutynin gel (Gelnique Transdermal) 10% - $16 per gram
- Oxybutyin Patch for Women (OTC) – Twice weekly dosing - $3.30 per patch
- Oxybutynin XL (Ditropan® XL) 5 mg #100 - $7.63 daily
- Oxybutynin ER (generic) - $6.25 daily
- Tolterodine IR (generic) – BID dosing - $2 to $6.80 daily
- Detrol ® IR - $9.25 daily
- Tolterodine ER (generic) - $6.75 to $10.80 daily
- Tolterodine ER (Detrol ® ER) - $14.67 daily
- Trospium IR – BID dosing - $1 to $5.60 daily (once daily dosing ClCr <30)
- Trospium ER - $6.75 - $10.77 daily (avoid in >75 y/o)
- Solifenacin (VESIcare®) - $15.42 daily
- Solifenacin (generic) - $0.57 - $14.65 daily
- Darifenacin (generic) - $11.06 daily
- Fesoterodine (Toviaz ®) - $15.06 daily
- Mirabegron (Myrbetriq®) - $17.20 daily

* Lexicomp pricing guide

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Other Considerations for Anticholinergics in Urge Incontinence

- Reduce trospium dose with ClCr ≤ 30 ml/min & avoid ER formulation with age ≥ 75
- Drug interactions
  - 50% reduction in dose of tolterodine, solifenacin, darifenacin and fesoterodine with potent CYP 3A4 inhibitors
    - Ex: Macrolide antibiotics (clarithromycin), imidazole antifungal agents, ritinovir
  - Tolterodine LA – antacids and PPIs
- Use in Alzheimer's disease
  - Enhanced sensitivity to CNS side-effects
  - Acetylcholinesterase inhibitors contribute to OAB
- Contraindicated in narrow angle glaucoma

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Role of Estrogens in Urge Incontinence

- Indicated for treatment of OAB associated with atrophic vaginitis or urethritis
- Oral therapy with estrogen and progestin – ineffective and may worsen OAB (Womens Health Initiative)
- Topical therapy with intravaginal estrogen tablets (63% improvement vs. 32% placebo)
- Recurrent vaginitis – estrogen cream applied one to two times per week

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Other Agents Used in Urge Incontinence

- Tricyclic antidepressants
  - Notripytyline (Aventyl®) or desipramine (Norpramin®)
  - No more effective than oxybutynin, more risk, use only as last resort
- Ineffective
  - Flavoxate (Urispas®)
  - Propantheline (Pro-Banthine®)
- Insufficient Information
  - Hyoscyamine (Anaspaz®)
  - Dicyclomine (Bentyl®)

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Other Agents for Urge Incontinence

- Mirabegron (Myrbetriq®)
  - Beta-3 receptor agonist
    - Relaxes detrusor muscle to increase bladder capacity
  - Similar in efficacy to tolterodine
  - No anticholinergic side effects – likely better tolerated
  - Adverse effects: HTN (8%), headache (3%)
  - Dose: 25 mg per day, may increase to 50 mg per day after 8 week
  - CYP2D6 Inhibitor – metoprolol, flecainide

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Pharmacotherapy of Stress Incontinence

- Alpha-1 receptor agonists
  - Ephedrine 25 mg bid (availability?)
  - Pseudoephedrine 15 to 45 mg tid
  - Duloxetine (off label) 20 mg bid then 40 mg bid after 2 wks
  - Toxicity
    - CNS stimulation
    - Caution in elderly with HTN, angina, or MI (relative contraindication)
    - Contraindicated in narrow angle glaucoma
- No more effective than bladder training therapy, pelvic floor muscle training (Kegel exercises) and pessaries

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Pharmacotherapy of Stress Incontinence

- Estrogen Therapy
  - No proven role for oral therapy
  - Topical therapy seems logical (insufficient evidence to determine its role)
- Combined estrogen therapy with alpha-agonists
  - Better than either alone
- Last resort – tricyclic antidepressants

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Overflow Urinary Incontinence

- Commonly associated with benign prostatic hyperplasia
- Non-drug interventions:
  - Lifestyle modification, reduced fluid intake, identify and treat reversible causes
  - Avoid exacerbating medications, alcohol and caffeine
- Medical therapies:
  - Alpha -1 receptor antagonists
  - Antiandrogens (5- αReductase Inhibitor)
  - Saw palmetto

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Alpha-1 Receptor Antagonists

- MOA: Relax smooth muscle tone in bladder neck, proximal urethra and prostate
- Terazosin (Hytrin®) – 1 to 5 mg q hs
- Doxazosin (Cardura®) – 1 to 5 mg q hs
- Tamsulosin (Flomax®) – 0.4 to 0.8 mg daily (30 minutes after the same meal each day)
- Alfuzosin (Uroxatral®) – 10 mg daily
- Silodosin (Rapaflo®) – 8 mg daily with a meal

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Alpha-1 Receptor Antagonists

- Response typically seen within two to three weeks of initiation or dose change
- Slight differences in adverse events profiles but all four appear to have equal clinical effectiveness (excluding silodosin)
- Postural hypotension – dose related and less likely with tamsulosin and alfuzosin (preferential binding in prostatic sites)

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Combination products

- Alpha blockers and 5-αRIs
  - Dutasteride (Avodart) and Tamsulosin (Jalyn®)
- Other therapy for LUTS with BPH
  - Tadalafil (Cialis®) – 5 mg/day

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Antiandrogen

- Finasteride (Proscar®)
  - MOA: 5 alpha-reductase inhibitor blocking conversion of testosterone to dihydrotestosterone reducing prostate hypertrophy
  - Decreases prostate size by ~25% - greatest effect with prostate enlargement
  - Symptom improvement: 30%
  - Dose: 5 mg per day
  - Maximum benefit: 6 to 12 months
- Dutasteride (Avodart®)
  - Dose – 0.5 mg per day

- Combination of alpha-1 receptor antagonist and antiandrogen –
  - Improve symptoms of BPH more effectively than either agent alone

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Alternative Remedies

- Saw Palmetto
  - MOA: Similar to fenasteride
  - Dose: 320 mg per day
  - Efficacy: Similar to fenasteride
  - Well tolerated > fenasteride
  - Nutritional supplement (not regulated and labeled as OTC) therefore purity and potency may vary between brands

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Supplements for Preventing Urinary Tract Infections

- UTI commonly associated with onset or worsening of incontinence
- Supplements touted to reduce UTI risk
  - Ascorbic acid
  - Cranberry
  - D-Mannose
- Not strongly supported by clinical data
- Despite lack of robust evidence of efficacy, no clinically important risk of harm

Song G, et al. Literature Review of Ascorbic Acid, Cranberry, and D-mannose for Urinary Tract Infection Prophylaxis in Older People. Sr Care Pharm 2023;38:315-28

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Conclusions

- Individualize management goals
- Select drug therapy based upon those individualized goals while considering:
  - Patient characteristics
  - Co-morbid disease states
  - Cost
  - Staff availability and training

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Updates in Managing Weight Loss in Older Individuals

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Learning Objectives

- List medications increasing risk of weight loss and describe the mechanism of the effect
- List medications increasing risk of weight gain and describe the mechanism of the effect
- Compare and contrast potential risks and expected benefits of medications commonly used to augment appetite and increase weight gain in elderly individuals

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Weight Loss in the Elderly

- Definitions
  - Sarcopenia: age-related decrease in muscle mass
  - Anorexia: decrease in appetite and oral intake
  - Dehydration: decrease in total body water due to reduced fluid intake or increased loss
  - Cachexia: loss of muscle and fat related to cytokine excess
  - Malabsorption: physiological abnormalities interfering in absorption of nutrients
  - Hypermetabolism: endocrine and disease-related processes increasing utilization

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Weight Loss in the Elderly Implications for Survival

- Higher Mortality
  - Predictive
  - Continued weight loss: 30% chance of death within 6 months
  - Weight stabilizes: 20% chance of death
  - Weight gain: 10% chance of death
- Federal definitions
  - Weight loss: 5% loss in 1 month or 10% loss in 6 months
  - Poor oral intake: consume less than 75% of most meals

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Factors Associated with Weight Loss in the Elderly
Meals on Wheels

M: Medications
E: Emotional/depression
A: Alcoholism
L: Late life paranoia
S: Swallowing problems

O: Oral factors - dentition
N: Nosocomial Infections

W: Wandering/dementia
H: Hyperthyroidism
Hypercalcemia
Hypoadrenalism
E: Enteral problems
E: Eating problems
L: Low salt, low cholesterol, therapeutic diet
S: Stones/cholecystitis

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Factors Associated with Weight Loss in the Elderly
Eleven "D's"

- Disease
- Dementia
- Delirium
- Drinking Alcohol
- Drug use
- Dysphagia
- Deafness or sensory deficit
- Depression
- Desertion
- Destitution
- Despair/depression

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Medications Associated with Weight Loss

- Nausea/vomiting: antibiotics, opiates, digoxin, theophylline, nonsteroidal anti-inflammatory drugs (NSAIDs), AChIs (donepezil, etc.)
- Anorexia: antibiotics, digoxin, AChIs (donepezil, etc.)
- Hypogeusia: metronidazole, calcium channel blockers, angiotensin-converting enzyme inhibitors, metformin
- Early satiety: anticholinergic drugs, sympathomimetic agents (e.g. modafinil - Provigil), nutritional supplements (ephedra, and ephedra-like agents, caffeine, caffeine analogs - bitter orange)
- Reduced feeding ability: sedatives, opiates, psychotropic agents
- Dysphagia: potassium supplements, NSAIDs, bisphosphonates, prednisolone
- Constipation: opiates, iron supplements, diuretics
- Diarrhea: laxatives, antibiotics
- Hypermetabolism: thyroxin, ephedrine

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Typical Strategies to Enhance Weight Gain

- Meal assistance
- Altering food texture/thickness
- Enteral feeding
- Meal supplements
- Pharmacologic interventions
  - Discontinuation of medications that may contribute to weight loss
  - Addition of medications promoting weight gain

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Medications used to Enhance Weight Gain

- Typical agents
  - Corticosteroids
    - Prednisone
    - Dexamethasone (Decadron®)
  - Progesterones
    - Megestrol (Megace®)
  - Cannabinoids
    - Dronabinol (Marinol®)
  - Antidepressants
    - Mirtazapine (Remeron®)
  - Antihistamines
    - Cyproheptadine (Periactin®)
  - Others

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Megestrol Acetate

- Formulations
  - Tablets: 20mg, 40mg
  - Suspension: 40mg/mL
  - Megace® ES: 125mg/mL
- Approved Indications
  - AIDS Cachexia:
    - 400-800mg daily for suspension
    - 625mg daily for Megace® ES
  - Palliative treatment of breast and endometrial cancer
    - Breast Cancer: 40mg 4 times daily
    - Endometrial Cancer: 40-320mg daily in divided doses; Max 800mg daily

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Megestrol Acetate

- Mechanism of Action
  - Inhibition of inflammatory cytokines
    - TNF-α, IL-1, IL-6, IL-8, IL-10
  - Potential androgen receptor modulator
- Enhanced appetite and mood in geriatric cachexia with no change in body composition (Yeh 2000)
- Potential Unintended/Adverse Effects
  - Adrenal insufficiency
  - Venous thromboembolism
  - Altered mental status
- Cost (per 400 mg dose): (Megace brand discontinued – generic only)
  - Oral suspension (40 mg/ml) $6.00
  - Oral suspension (125mg/ml) $5.00
  - Megestrol tablets (40 mg) $3 to $17
  - Megace ES oral solution (625mg/5ml) $24 (discontinued)

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Megestrol Acetate: Outcomes in Elderly Patients

- Evaluated effect of megestrol acetate on food and fluid intake in nursing home patients receiving optimal feeding assistance vs. those receiving standard care
- Treatment
  - Megestrol acetate suspension 400mg daily for 63 days
  - Optimal feeding assistance weeks 2, 4, 6
    - 31.0 ± 7.54 minutes of staff assistance per meal
  - Usual care weeks 1, 3, 5
    - 2.8 ± 4.0 minutes of staff assistance per meal
- Results:
  - Megestrol acetate in the absence of optimal feeding assistance, was not effective at increasing oral food and fluid intake in nursing home residents; megestrol acetate is effective in improving oral intake only when used in combination with optimal mealtime feeding assistance

Simmons S, et al. The effect of megestrol acetate on oral food and fluid intake in nursing home residents: a pilot study. *Journal of the American Medical Directors Association.* 2004: 5(1), 24-30.

90

Megestrol Acetate: Outcomes in Elderly Patients

- Investigate optimal dosing and efficacy of megestrol acetate for elderly patients with impaired appetite post-hospitalization
- Treatment groups
  - Placebo (n=12)
  - 200mg megestrol acetate daily (n=12)
  - 400mg megestrol acetate daily (n-12)
  - 800mg megestrol acetate daily (n=11)
- Primary Outcome - Appetite
  - 20-day point, 800mg treatment group: Appetite better than at baseline (P=0.04)
  - 42-day point, 400mg treatment group: Appetite at start of last meal better than at baseline (P=0.02)
  - No differences between treatment groups for any of the appetite measures

Reuben et al. The Effects of megestrol acetate suspension for elderly patients with reduced appetite after hospitalization: a phase II randomized clinical trial. *The Journal of the American Geriatric Society.* 2005: 53(6), 970-5.

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Megestrol Acetate: Outcomes in Elderly Patients

- Albumin
  - No significant changes from baseline for any of the treatment groups
- Prealbumin
  - At 20-days: Significant increases in prealbumin compared to placebo in only the 400mg and 800mg groups
  - At 62-days: Significant increase in prealbumin compared to placebo only in the 400mg treatment group
- Adverse effects
  - No patients developed clinical symptoms of adrenal insufficiency
  - 3 patients developed diarrhea (2 in 400mg group, 1 in 800mg group)
  - 1 patient developed DVT (in 200mg group)
  - 1 patient developed DVT with multiple PEs (in 400mg group)

Reuben et al. The Effects of megestrol acetate suspension for elderly patients with reduced appetite after hospitalization: a phase II randomized clinical trial. *The Journal of the American Geriatric Society.* 2005: 53(6), 970-5.

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Megestrol Acetate: Outcomes in Elderly Patients

- Megestrol acetate 400mg and 800mg doses increase prealbumin in recently hospitalized older persons
- Cortisol suppression was common and may be persistent at higher doses
- Additional benefit for other nutritional or clinical outcomes (e.g. weight) was not observed

Reuben et al. The Effects of megestrol acetate suspension for elderly patients with reduced appetite after hospitalization: a phase II randomized clinical trial. *The Journal of the American Geriatric Society.* 2005: 53(6), 970-5.

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Megestrol Acetate: Outcomes in Elderly Patients

- Examine the effects of megestrol acetate on weight and overall mortality in elderly nursing home residents
- Study process:
  - 17,328 nursing home residents identified through MDS (minimum data set) database
  - 709 residents receiving ≥ 7 days of megestrol acetate treatment within 30 days of defined index event were matched (1:2) with 1418 residents not treated with megestrol acetate who were alive within 30 days of defined index event
  - Matching included: Age, sex, race, index date, index date, index weight, ADLs, cognitive function, unstable condition, acute episode of current problem, end-stage disease, number of medications during previous 7 days, cancer diagnosis, HIV diagnosis

Bodenner D, et al. A retrospective study of the association between megestrol acetate administration and mortality among nursing home residents with clinically significant weight loss. *The American Journal of Geriatric Pharmacotherapy.* 2007: 5(2), 137-146.

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Megestrol Acetate: Outcomes in Elderly Patients

- Primary outcome – mortality
  - 23.4% decrease in median survival in megestrol acetate group vs. control group
  - Megestrol group – median survival
    - 23.9 months (95% CI 20.2-27.5)
  - Control group – median survival
    - 31.2 months (95% CI 27.8-35.9)
  - Median survival times were not statistically significant between differing megestrol acetate dosages
    - Compared <200mg/day, 200-400mg/day, >400mg/day

Bodenner D, et al. A retrospective study of the association between megestrol acetate administration and mortality among nursing home residents with clinically significant weight loss. *The American Journal of Geriatric Pharmacotherapy.* 2007: 5(2), 137-146.

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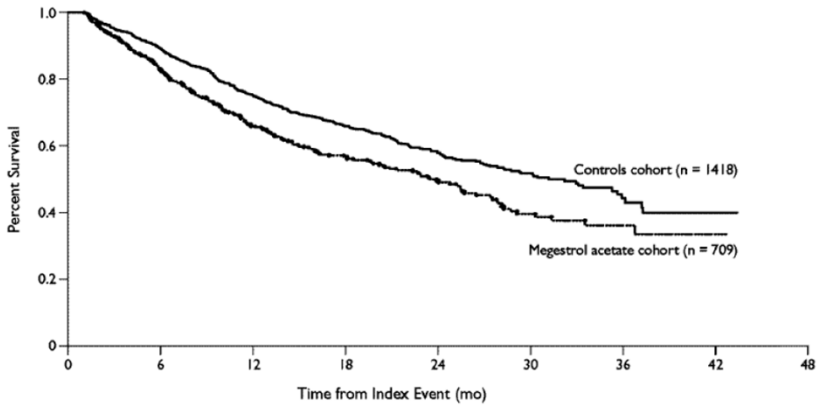
Megestrol Acetate: Outcomes in Elderly Patients



Bodenner D, et al. A retrospective study of the association between megestrol acetate administration and mortality among nursing home residents with clinically significant weight loss. *The American Journal of Geriatric Pharmacotherapy.* 2007: 5(2), 137-146.

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Dronabinol

- Formulations: Marinol®, and generic capsules
- Indication: AIDS-related appetite stimulation, antiemetic (chemotherapy)
- Dosing: start 2.5 mg BID (AC lunch and dinner) up to 20mg/day
- Adverse effects: significant CNS depression, dependency (esp. in those with history of other drug/alcohol abuse), caution in those with psychiatric disorders, lowers seizure threshold; use with caution in elderly, may cause postural hypotension
- Cost: $2 to $45 per capsule (generic) $14 to $47 per capsule (brand)

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Dronabinol Outcomes in Weight Loss

- Improved mood and appetite in cancer patients and AIDS cachexia; no significant increase in weight
- May reduce agitation in patients with Alzheimer's disease and increasing weight (Volicer 1997)
- May increase risk of delirium; start low and increase dose slowly
- Used to treat intractable nausea and vomiting
- Resulted in greater appetite and weight gain in cancer-associated anorexia than megestrol (Jatoi 2002)

Thomas DR. Anorexia: Aetiology, epidemiology and management in older people. Drugs Aging 2009;26:557-570.

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Mirtazipine

- Formulations: Remeron®, Remeron® SolTab, generic tablets
- Mechanism:
  - Enhances central NE and 5HT activity
  - Also blocks histamine receptors
    - Sedative properties (especially at low doses)
  - Mild appetite stimulation properties
- New FDA 'Black Box' warning of cardiac dysrhythmias (QT prolongation & Torsades de Pointes)
- Cost: $2-3 (generic) $7-8 (Brand)

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Mirtazipine Outcomes in Weight Loss

- Treating depression improves mood and appetite
- Tricyclic antidepressants and MAO inhibitors historically cause significant weight gain but have significant risk (especially in elderly)
- Mirtazapine studies show weight gain as most common adverse effect in studies
- No difference in weight change at 3 and 6 months noted between mirtazapine and all other nontricyclic antidepressants – except fluoxetine (Mihara 2005)

Thomas DR. Anorextia: Aetiology, epidemiology and management in older people. Drugs Aging 2009;26:557-570.

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Other Agents

- Corticosteroids (prednisone, dexamethasone)
  - Increased appetite in randomized trials without significant weight gain
- Cyproheptadine (Periactin®)
  - Increased appetite in cancer patients without weight gain
- Thalidomide (Thalomid®)
  - Produces weight gain in some patients with HIV-associated wasting syndrome
- Medroxyprogesterone (Provera®)
  - Produces weight gain when used in chemotherapeutic regimens, independent of tumor response

Thomas DR. Anorexia: Aetiology, epidemiology and management in older people. Drugs Aging 2009;26:557-570.

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Other Agents

- Anabolic hormones –
  - Testosterone
    - Replacement leads to increased muscle mass and strength; may enhance functioning
  - Oxymetholone
    - Produces weight gain in advanced HIV-1 infection but not cancer patients
- Human growth hormone
  - Increased weight in AIDS patients; required higher than physiological doses
  - Improved nitrogen retention in older patients but associated with increased mortality

Thomas DR. Anorexia: Aetiology, epidemiology and management in older people. Drugs Aging 2009;26:557-570.

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Summary

- Positive results of weight gain and enhanced appetite in geriatric anorexia or cachexia is not strongly supported by published evidence for commonly prescribed appetite stimulants
- Megestrol is listed on the BEERs List as a potentially inappropriate drug due to increased risk of adverse effects and mortality with questionable benefit; benefit likely enhanced with optimized feeding assistance
- Dronabinol may increase weight and have beneficial effects on agitation in patients with dementia, but carries significant risk of delirium in older individuals

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Summary (continued)

- Although mirtazapine is commonly used as an appetite stimulant, other SSRI antidepressants are likely to result in similar weight gains by treating depression in elderly patients; fluoxetine may result in higher weight gains but long duration of action may be associated with increased risk of adverse effects in the elderly (Previously listed on the BEERS List).
- Other agents have shown benefit in selected populations but risks must be considered before using in a frail elderly patient.

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Current Trends and Recommendations for Anticoagulation in Older Individuals

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Presentation Objectives

- Recommend first line anticoagulant therapies in elderly individuals for common conditions and indications
- Compare potential benefit and risk of Direct Oral Anticoagulants (DOACs) against warfarin in individuals with atrial fibrillation
- Suggest situations where continued or combination use of anticoagulants may be associated with significant risk in elderly individuals

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Current Anticoagulant Recommendations for AFIB in Elderly Individuals

- Significant changes and updates in recent years
  - Adoption of DOACs over warfarin in most situations
  - Warfarin still recommended in specific situations

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Stroke Prevention

- CHA_2DS_2-VASc - calculates stroke risk for patients with atrial fibrillation, possibly better than the CHADS2 score
  - Adds gender, more points for advanced age and adds vascular disease history
- Helpful tools but use common sense.
  - If increased fall risk or other risk of hemorrhage recommend antiplatelet therapy. Another example might be a patient with MCI who lives alone.
- HAS-BLED score - developed as a practical risk score to estimate the 1-year risk for major bleeding in patients with atrial fibrillation

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Direct-Acting Anticoagulants

- Recent treatment guidelines and 2022 AGS Beers Criteria now recommend apixaban over warfarin due to increased efficacy and lower risk
- Oral factor Xa inhibitors
  - Apixaban (Eliquis®) – preferred agent
    - Adjust dose: age ≥ 80 AND ≤60 kg or SCr ≥1.5mg/dl
  - Rivaroxaban (Xarelto®) – not recommended (BEERS)
  - Edoxaban (Savaysa®)
- Direct thrombin Inhibitor
  - Dabagatran (Pradaxa®) – use with caution - altered kinetics in elderly

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Assessing Bleeding Risk with Anticoagulation

- Typical risk assessment using HAS-BLED scoring rubric
- Newer guidelines from Royal College of Physicians recommend ORBIT Bleeding Risk Score for Atrial Fibrillation (ORBIT Bleeding Risk Score for Atrial Fibrillation (mdcalc.com) based on higher accuracy in predicting absolute bleeding risk
- Increased risk
  - Uncontrolled HTN
  - Concurrent medications (antiplatelets, SSRIs, NSAIDS)
  - Harmful alcohol consumption
  - Reversible causes of anemia

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Bleeding Risk with Combination Anticoagulation Therapies

- Warfarin alone:
  - 2-fold estimated risk of hemorrhagic complications
  - Major bleeding risk 0.3% to 0.5% per year
  - Risk higher with venous thromboembolism than with AFIB
  - 2-fold increased risk with INR >3.0 vs. INR between 2.0 and 3.0
- Warfarin plus ASA:
  - Hemorrhage risk HR: 2.5 [95% CI 1.7 to 3.7]

Shoeb M & Fang MC. J Thromb Thrombolysis. 2013 April ; 35(3): 312–319

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Bleeding Risk with Combination Anticoagulation Therapies

- Case control study of over 23,000 new DOAC users
- Major bleeding events in 393 out 23492 treated patients (1.67%)
- Increased risk with concomitant use of antiplatelet agents and SSRIs [OR 1.92; (95% CI, 1.40–2.66)]
  - Antiplatelets: OR 2.01 (95% CI, 1.29–3.11)
  - SSRIs: OR 1.68 (95% CI, 1.10–2.59)
  - Inadequate numbers to assess ‘triple’ therapy

Zhang Y, et al. Br J Clin Pharmacol 2020;86:1150-1164.

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Addressing Risk and Benefit – A Case Example

- 89 y/o Woman admitted three years ago to a local Assisted Living Facility (ALF)
- Hx:
  - Hip Fx (3 yrs ago)
  - HTN
  - Hyperlipidemia
  - CAD w/CABG (~20 yrs ago)
  - AFIB
  - COPD
  - Dementia
  - Depression

Medications:

- Amlodipine + Losartan + Metoprolol + Digoxin
- Simvastatin + Omega 3
- Clopidogrel + ASA + Apixaban
- Furosemide +KCl
- Famotidine
- Calcium/D + Vit E + Folic Acid
- Fluticasone/Salmeterol
- Memantine
- Fluoxetine + Sertraline

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Addressing Risk and Benefit – A Case Example

- Initial thoughts?
- What is the greatest risk to this individual?
- Focusing on anticoagulation –
  - Any specific thoughts?
  - Do you have an estimate of her stroke risk?
  - What if I told you she was admitted last year with an evolving stroke that responded well to acute antithrombotic therapy?
  - What is her risk for a major bleeding episode?
  - Any options to simplify her current 'triple therapy'?
- What changes are expected with increasing frailty?

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Final Thoughts and Questions

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Managing Major Geriatric Syndromes - Fact, Fiction, Updates and Clinical Pearls

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Walter P. Scheffe CPE Series
October 28, 2023

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