Dementia Pharmacotherapy
early therapeutic interventions can maximize pharmacologic efficacy with these agents
Selecting a Medication

- Not enough evidence to recommend one agent over another based on efficacy
- No way to determine if or how a particular patient will respond to therapy
- Guidelines suggest initiating therapy early, as soon as diagnosis is made, to maximize clinical benefits
Treatment Considerations

- Decision to initiate treatment and the choice of agent must be individualized
  - Potential benefit
  - Cost
  - Comorbid conditions

- If pharmacotherapy is initiated, benefit should be seen within three months
  - Treatment considered **successful if memory remains unchanged for 6 months**
Goals for the Treatment of Alzheimer’s

• Improve memory
• Improve functional status
• Improve behavioral symptoms
• Slow progression
• Delay or prevent onset
Impact of Coexisting Medical Conditions

2.4 conditions/pt
- HTN 82%
- DM 39%
- CAD 21%
- CHF 14%
- Stroke 10%

Prevalence of coexisting conditions in PWD

Prevention, Risk Reduction, and/or Optimizing Brain Health?

- **Social, mental, and physical activity** shown to be inversely associated with risk for dementia and AD
- **Exercise** speculated to enhance brain neurotrophic factors and modify apoptosis
- Longitudinal cohort studies show risk of AD increased among people who have received **shorter periods of education**
- **Intellectually challenging activity** has been associated with reduced risk of dementia in longitudinal studies
- Reasonable to encourage patients to maintain or increase **physical activity, exercise, cognitive and leisure activities, and social interaction**, though it is not known whether these interventions reduce dementia risk
Interventions That *Might* Prevent or Delay AD

- Antihypertensive therapy
- Hormonal agents (estrogen)
- NSAIDs (naproxen and celecoxib)
- High-dose vitamin B, folic acid supplementation
- Statins
- PPAR-gamma agonists
- Fish oil, omega 3 fatty acids
- Weight control, healthy diet
Benefit of Therapy

# Pharmacologic Treatments for AD

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<th>MOA</th>
<th>Cholinesterase Inhibitors</th>
<th>NMDA-Receptor Antagonist</th>
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<td><strong>Drug</strong></td>
<td><strong>Donepezil</strong></td>
<td><strong>Galantamine</strong></td>
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<td><strong>Indication</strong></td>
<td>Mild-moderate AD; severe AD</td>
<td>Mild-moderate AD</td>
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<td><strong>Initial dose</strong></td>
<td>Tablet: 5 mg qd</td>
<td>Tablet/oral solution: 4 mg bid</td>
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<tr>
<td></td>
<td>ER capsule: 8 mg qd</td>
<td>Patch: 4.6 mg qd</td>
</tr>
<tr>
<td><strong>Maximal dose</strong></td>
<td>Tablet: 10 mg qd</td>
<td>Tablet/oral solution: 12 mg bid</td>
</tr>
<tr>
<td></td>
<td>ER capsule: 24 mg qd</td>
<td>Patch: 9.5 mg qd</td>
</tr>
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</table>

ER = extended-release; MOA = mechanism of action; NMDA = N-methyl-D-aspartate.

Cholinesterase Inhibitor Therapy in AD

**Disease Severity**

- **MCI**
  - Benefits cognition?

- **Early-Stage Dementia**
  - Benefits cognition

- **Moderate Dementia**
  - Benefits cognition
  - Preserves global status
  - Preserves ADLs
  - Benefits behavior?

- **Severe Dementia**
  - Benefits cognition
  - Preserves global status
  - Preserves ADLs
  - Benefits behavior?

Class approved for mild-moderate AD
Donepezil also approved for severe AD
Memantine Therapy for AD*

- MCI: Role unknown
- Mild-Moderate Dementia: Inconsistent effects
- Moderate-Severe Dementia: Benefits cognition, Preserves global function, Preserves ADLs, Benefits behavior

*Approved for moderate-severe AD in the U.S., alone or in combination with cholinesterase inhibitors
Routine clinical practice often combines a cholinesterase inhibitor with memantine, and recent studies have shown that this combination may provide beneficial response compared with only cholinesterase inhibitor pharmacotherapy.
In long-term use, they slow the progression of memory loss and diminish:
- apathy,
- depression,
- hallucinations,
- anxiety, euphoria,
- and purposeless motor behaviors.
Donepezil and rivastigmine may be beneficial for patients with Parkinson's disease and Lewy body disease and for treatment of cognitive deficits caused by traumatic brain injury.

Occasionally, cholinesterase inhibitors elicit an idiosyncratic catastrophic reaction, with signs of grief and agitation, which is self-limited after the drug is discontinued.
Donepezil
Donepezil

- The half-life of donepezil is 70 hours in elderly persons, and it is taken only once daily.
- 3% GI problems (nausea, diarrhea, and vomiting)
- Bradyarrhythmias (Syncope)
- Weight loss
- 10-mg dose than with a 5-mg dose
Donepezil

- donepezil appears to be selectively active within the CNS and has little activity in the periphery.
- Donepezil's favorable side effect profile appears to correlate with its lack of inhibition of cholinesterases in the GI tract.
Rivastigmine
The half-life is 1 hour, but because it remains bound to cholinesterases, a single dose is therapeutically active for 10 hours, and it is taken **twice daily**.
Rivastigmine appears to have somewhat more peripheral activity than donepezil and is thus more likely to cause GI adverse effects than is donepezil.
There was no evidence of hepatotoxicity

Fewer adverse events were observed with concomitant food administration versus administration without food

In addition to nausea and vomiting, rivastigmine was associated with significant weight loss
Positive effects on ADL have been observed in some studies.

Rivastigmine is generally safe and well tolerated, although cholinergic side effects occur at high doses.
Galantamine
Galantamine (Reminyl®)

- Galantamine has a dual mechanism of action
  - Competitive inhibition of acetylcholinesterase\(^1\)
  - Allosteric modulation of presynaptic and postsynaptic nicotinic receptors\(^2\)
- Galantamine improves major aspects of AD (eg, cognition, behavior, function)\(^1\)
- Galantamine is generally safe and well tolerated\(^1\)
- 8 mg/day for 4 weeks, 16 mg/day for 4 weeks (maintenance), 24 mg/day maximum recommended dose
Dual Mechanism of Action

Presynaptic nerve terminal

M receptor

N receptor

Galantamine

Postsynaptic nerve terminal

M receptor

N receptor

N = nicotinic
M = muscarinic
ACh = acetylcholine
Galantamine: Potential Advantages of Nicotinic Receptor Modulation

- May increase release of ACh
  - Release of other neurotransmitters also increases
- May have a neuroprotective effect
GI Adverse Events

- Nausea: incidence related to treatment initiation and dose escalation
  - Typically transient, resolving within 1 week
  - Rarely severe
- Weight loss: reported as an adverse event in ~5% of patients, with none discontinuing treatment
Comedication

- Minimal potential for clinically relevant drug interactions
  - No effect on kinetics of digoxin or warfarin
- As with other cholinergics, galantamine should be used with caution in patients with heart block or sick sinus syndrome
Medications to Avoid

• Review patient profile for medications that can temporarily cause or worsen symptoms of AD

• Medications with strong anticholinergic side effects
  
  ▪ Effects are additive: more drugs = more likely to cause mental status change

  ▪ Anticholinergic medications and cholinesterase inhibitors antagonize each other!
Medications to Avoid: Examples

- **Antiemetics**
  - Dimenhydrinate, meclizine, promethazine, scopolamine

- **Tricyclic Antidepressants**
  - Amitriptyline, doxepin, imipramine, nortriptyline

- **Antiparkinsonian Anticholinergics**
  - Benztropine, trihexyphenidyl

- **Antipsychotics**
  - Clozapine, olanzapine, thioridazine, chlorpromazine

*Preferred antipsychotic agents when used to treat behavioral problems in elderly with dementia include: Haloperidol & Risperidone*
Medications to Avoid: Examples

• **Antihistamines**
  - Diphenhydramine, chlorpheniramine, hydroxyzine

• **Anxiolytics**
  - Benzodiazepines (diazepam, alprazolam, etc.)

• **GI/Urinary Antispasmodics**
  - Atropine, scopolamine, dicyclomine, hyoscin, oxybutynin, tolterodine

• **Muscle Relaxants**
  - Cyclobenzaprine, metaxolone, tizanidine
Monitoring

- Improvement in cognitive performance
  - MMSE & caregiver impression at 4 to 6 weeks then every 6 months

- Bradycardia or AV block

- Gastrointestinal bleeding; especially with history of ulcer disease or concomitant NSAID use

- Hepatic and renal function

- Body weight (rivastigmine)
NMDA Antagonist: Memantine

• N-methyl-D-aspartate (NMDA) receptor antagonist

• Modifies function of NMDA brain receptor to ↓ the negative effect of having too much exposure to the brain chemical glutamate

• Appears to be neuroprotective
Memantine

- Used in moderate-severe dementia
  - Little evidence that patients with milder disease benefit from memantine

- Appears to have fewer side effects than acetylcholinesterase inhibitors
  - Dizziness is the most common side effect
  - Increase agitation and delusional behaviors in some patients
  - Confusion and hallucinations have been reported in a small amount of patients
Switching ChEIs

- Lack or loss of therapeutic benefit
- Immediate switch
  - No washout needed

- Tolerability issues
  - Washout period of 1-2 weeks before starting another agent

- Noncompliance
  - Try an alternate dosage form before switching
The combination of an AChEI and memantine can be used in advanced disease or if the person does not respond to an AChEI by itself.

Namzaric, a fixed-dose combination of extended-release memantine and donepezil approved in December 2014.
Other Medications

Lack of evidence or positive outcomes associated with the following agents discourages their use for treatment of AD (until further data is available):

- Estrogen-based therapy
- Vitamin E (α-tocopherol)
- Selegiline
- Anti-inflammatory drugs
- Ginkgo biloba
Discontinuation of Therapy

- Clinical controversy: when to discontinue therapy?

- Generally administer for 8-12 weeks at recommended or maximum tolerated dose

- Review patient’s response with family/caregivers
  - Continue treatment if benefit is noted either on bedside testing or by the family/caregiver

- Consider stopping treatment if:
  - No benefit, poor compliance, persistent side effects (diarrhea, bradycardia, weight loss, etc.), severe decline in functional status, hepatic failure

Severe loss in functional status (e.g. speech is limited and noncommunicative, ambulation is no longer possible, ability to hold up head independently is lost)

Bradycardia < 50 BPM

Severe hepatic impairment (Child-Pugh >/= 10)

Failure to tolerate the minimum effective dose
Discontinuation of Therapy

- Data for optimal duration of treatment as disease progresses is limited
  - Modest cognitive and functional benefits associated with continued therapy with (donepezil) in moderate to severe AD\(^1\)
  - Discontinuation associated with adverse behavioral changes and reduced participation in activities\(^2\)