Pharmacotherapy for Alzheimer’s Disease

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Tennessee’s Basketball Head Coach Pat Summitt Diagnosed with Early-Onset Alzheimer’s Disease at Age 58
Alzheimer’s Disease

- First described in 1906 by Dr. Alois Alzheimer during brain autopsy in a 51-yo with memory impairment
- Characterized by dementia – a precipitous decline in cognitive function not part of normal aging
  - Alzheimer’s is the most common cause of dementia (60%)
- Early onset disease: 40 to 64-yo; 5% of cases
- Late onset disease: ≥ 65-yo
  - 4% in ages 65 - 74 years
  - 20% in ages 75 - 84 years
  - 50% in ages > 85 years

Alzheimer’s Disease Epidemiology

- Afflicts 4 million Americans
  - 14 million by the year 2050
- A fatal disease
  - Fourth leading cause of death in the US
  - Average survival following Dx is 5 - 10 years
  - Death due to aspiration, trauma, cachexia
- 3rd most expensive disease in the US
  - $100 billion per year in treatment costs

Genetic Links to Early-Onset Alzheimer’s Disease

- Alterations in Chromosomes 1, 14, or 21
- Chromosome 14
  - Aggressive early-onset AD
  - presenilin 1 & 2 involved in Amyloid Precursor Protein (APP) synthesis
- Chromosome 21
  - Amyloid precursor protein
  - Down’s Syndrome have 3 copies
- Chromosome 19 responsible for APO E production
  - 40% of late-onset AD have at least one copy of APO E4
  - 90% with 2 copies of E4 will develop AD by 80 yo
The genetic test for predicting your risk of early onset - ages 40 – 65, and aggressive AD is available. Would you like to have the DNA test performed to learn your risk for early-onset Alzheimer’s Disease?

A. Yes - perform the test, I want to know
B. No – do not perform the test, I do not want to know

Alzheimer’s Disease in Skilled Nursing Facilities
1.8 Million Patients in SNFs

- 50% incidence rate for AD
- 22% of those with AD are diagnosed
- 30% of those diagnosed are treated
- 6% - 7% of AD patients are receiving AD-specific treatment

Disease-Induced Dementia

- Stroke (15%)
- Infections (HIV)
- Parkinson’s Disease
- Huntington’s Dz
- Creutzfeldt-Jakob Disease
- Multiple Sclerosis
- Head Trauma
- Encephalopathy
- Intracranial
  - Tumors
  - Hematomas
  - Hydrocephalus
- Depression
- Hypothyroidism
- Hypoglycemia
- B<sub>12</sub> deficiency
- Folic acid Deficiency
Which of the following agents can cause drug-induced dementia?

A. Cyproheptadine  
B. Amitriptyline  
C. Diphenhydramine  
D. All of the above

Drug-Induced Dementia

- Clonidine
- Methyldopa
- Guanfacine
- Reserpine
- Aluminum
- Cocaine
- Ethanol abuse
- Phencyclidine
- Lysergic Acid Diethylamide

- Anticholinergics
  - TCAs
  - Antipsychotics
  - Diphenhydramine
  - Clemastine
  - Hydroxyzine
  - Benztrapine
  - Amantadine
  - Trihexyphenidyl
  - Ophthalmics

Anticholinergics
May antagonize Cholinesterase inhibitors

- Antispasmodics
  - Belladonna Alkaloids
  - Clidinium
  - Dicyclomine
  - Flavoxate
  - Hyoscyamine
  - Oxybutynin
  - Propantheline
  - Torderine

- Sedative/Hypnotics
  - Barbiturates
  - Meprobamate
  - Cyproheptadine
  - Dimenhydrinate
  - Meclizine
  - Trimethobenzamide
  - Diphenoxylate/Atropine
### Serum Anticholinergic Activity

<table>
<thead>
<tr>
<th>Medication</th>
<th>ng/mL Atropine Equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>0.86</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.55</td>
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<tr>
<td>Theophylline</td>
<td>0.44</td>
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<tr>
<td>Digoxin</td>
<td>0.25</td>
</tr>
<tr>
<td>Furosemide</td>
<td>0.22</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>0.22</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.22</td>
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<tr>
<td>Warfarin</td>
<td>0.12</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.11</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>0.11</td>
</tr>
</tbody>
</table>

### Pathophysiology of Alzheimer's Disease

- **Amyloid Cascade Hypothesis (Early-onset AD)**
  - Neuritic Plaques - extracellular
    - Consist of β amyloid proteins formed by β-secretase
  - Neurofibrillary Tangles - intracellular
    - Abnormally phosphorylated tau protein causing microtubules to collapse
- **Cytokines and the inflammatory process**
  - IL1-α, IL-β, IL-6, TNF-α, interferon

© Neurofibrillary Tangles

© Neuritic Plaques
Cerebral Atrophy

Normal Brain

Alzheimer’s Disease

Pathophysiology of Alzheimer’s Disease

- Cholinergic Hypothesis
  - Decreased choline acetyltransferase and AChE
  - Dysregulated Glutamate Activity
    - Involved in memory and learning
    - Agonist on N-methyl-D-aspartate receptor
    - Prolonged synaptic glutamate concentrations destroy nerve cells
  - MAO type B activity is increased
  - Increased oxidative stress and free radicals
  - Free radical formation

Neuropathological Signaling: Cholinergic Hypothesis

ACh = acetylcholine; AChE = acetylcholinesterase; BuChE = butyrylcholinesterase

Adapted from Adem A. Acta Neurol Scand. 1992;85(suppl 139):69-74.
Clinical Features of Alzheimer's Disease

- Subtle but progressive loss of cognitive function
- Loss of memory, language, judgment, praxis and orientation
  - Inability to retain new information
  - Information retrieval
  - Immediate recall is retained until late AD
- Aphasia – generally late AD
  - Palilalia – continuous repetition of words
  - Echolalia – repeating what others have said

Clinical Features of Alzheimer's Disease

- Visuospatial abilities are lost
- Behavioral symptoms
  - Anxiety, peevish, cantankerous, delusions, hallucinations, aggression, depression, suspiciousness and psychosis
- Sleep disturbances
- Weight loss and nutritional deficiencies
- Functional impairment

Diagnosis of Alzheimer's Disease

- Formerly a diagnosis of exclusion
- AD can only be confirmed by examination of brain tissue at autopsy or biopsy
- Must R/O other causes of dementia
  - Patient Hx, medication Hx, Physical, VDRL, anemia profile – B12, folate, TFTs, LETs, renal function, blood glucose, CT scan, MRI
- Comprehensive Drug Regimen Review
- Psychometric Evaluation and Psychiatric Evaluation
- Must meet the criteria of the NINCDS-ADRDA: Probable Alzheimer’s Disease
**DSM-IV Definition of AD**

- Memory impairment
- One or more of the following:
  - Aphasia
  - Apraxia (impairment of motor skills)
  - Agnosia (failure to recognize familiar objects)
  - Disturbances of executive functioning
- Insidious onset and continued decline
- Decline from previously higher level of function
- Negative laboratory evaluation

**The 7 Warning Signs of AD**

1. Asking the same question over and over again
2. Repeating the same story word for word
3. Forgetting how to perform common tasks previously performed with ease
4. Losing the ability to pay bills or balance a check book
5. Getting lost in familiar surroundings and misplacing household objects
6. Neglecting to bathe or change into clean clothes while insisting they have taken a bath or that the clothes are clean
7. Relying on someone else, such as a spouse, to make decisions or answer questions

**When should patients be screened for AD?**

- Conduct test for patient if:
  - Caregiver describes a memory problem
  - Patient complains of decline in memory
  - Patient is unable to answer usual medical history questions
- Perform tests for all new patients > 65 years old to establish baseline

DSM-IV is the Diagnostic and Statistical Manual for Mental Disorders (fourth edition).
Two Key Screening Tests

1. Folstein Mini-Mental State Examination
2. Clock Drawing


Mini-Mental State Exam

The Folstein Mini-Mental State Examination (MMSE) has a scoring range from 0 - 30, with the following scoring key:

28 - 30 = normal
25 - 27 = possible mild cognitive impairment
19 - 26 = mild dementia
10 - 18 = moderate dementia
0 - 9 = severe dementia

Clock Drawing Instructions

1. First draw a large circle for the patient on a blank sheet of paper.
2. Next, ask the patient to insert all the numbers that regularly go on a clock.
3. Third, ask the patient to draw where the hands of the clock should go if the time were 10 minutes until 2:00.
Clinical Expression of AD in Residential Care

- **Cognition**
- **Behavior**
- **Function**

Unique Symptom Pattern of AD

Goals of Pharmacotherapy

- Reduce effects of the illness
- Restore lost human connection and self-respect
- Lengthen period of self-sufficiency
- Delay need for higher level of care or nursing home placement
- Reduce caregiver burden
**Tacrine (THA; Cognex®) (approved 1993)**
- A competitive, reversible inhibitor of AChE and BChE
- ACh, NEPI, 5-HT, GABA, dopamine
- Indication: Tx of mild to moderate dementia of the Alzheimer’s type
- One trial demonstrated that 3 months of Tx results in 6 months of reversal of progression
- Due to hepatotoxicity limited use and refractory
- GI: N,V,D; ataxia and tremor: 20% withdrawal rate
- Dosed QID – poor compliance

**Goal Of Cholinesterase Inhibitors**
- Slow the rate of decline in cognitive, functional, and behavioral domains
- Until memantine, the only FDA approved medication for mild to moderate AD
- Accumulating data for efficacy in severe AD

**Donepezil (Aricept®) – approved 1996**
Mr. Zuck is a 83-yo active male pharmacist diagnosed with mild to moderate Alzheimer’s Disease. Which of the following regimens should be initiated at this time?

A. Donepezil 5 mg daily  
B. Donepezil 23 mg daily  
C. Memantine  
D. Donepezil plus memantine

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Donepezil (Aricept®) – approved 1996

- Centrally acting reversible AChEI
- High specificity for AChE & not BChE
- May account for less ADEs
- Indication: Tx of mild to moderate dementia of the Alzheimer’s type
- Clinical trials demonstrate efficacy with the 5 mg qd dose (Mean age of trials was 73 yo)
- Efficacy sustained for 2 years

- Global scores worsen indicating that donepezil does not completely prevent disease progression

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Long-Term Donepezil Treatment in Mild to Moderate AD

Results: Cognitive — MMSE

<table>
<thead>
<tr>
<th></th>
<th>Donepezil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>End Point</td>
<td>91 (135)</td>
<td>98 (137)</td>
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<tr>
<td>92</td>
<td>104</td>
<td>105</td>
</tr>
<tr>
<td>93</td>
<td>106</td>
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<td>94</td>
<td>107</td>
<td></td>
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<tr>
<td>95</td>
<td>108</td>
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</table>

P=.053 P=.001 P=.019 P=.001 P<.001*
**Donepezil Pharmacokinetics**

- $T_{1/2} = 70 – 80$ hours
- Steady state achieved in 14 - 21 days
- $F = 100\%$; food has no effect
- Renally eliminated
  - $\approx 60\%$ of parent in urine
  - Levels were similar among young and old
- Metabolized by CYP450 2D6 and 3A4
  - 2 metabolites are active
  - Linear metabolism
  - Levels not altered by liver cirrhosis

**Donepezil Adverse Effects and Dosing**

- ADEs are mild and transient
- Nausea, diarrhea, fatigue, vomiting, anorexia, muscle and leg cramps
- No hepatotoxicity reported!
- 5% discontinuation rate (placebo 5%)
- Rapid dose escalation led to 13% discontinuation
- Dose: 5 and 10 mg film-coated tablet or ODT qd PM
  - Begin with 5 mg for 4 weeks
  - Some patients may require 10 mg qd
  - May increase dose from 5 to 10 mg in 4 – 6 weeks

**Aricept Film Coated Tablets**

- 5 mg and 10 mg (~$8/dose each)
Aricept Orally Disintegrating Tablets (ODT) 5 mg and 10 mg (~$8 dose)

- Allow tablet to dissolve completely on tongue and follow with water

Aricept® 23 mg Tablet
FDA approved July 26, 2010

- Indicated for moderate to severe AD
- Before starting Aricept 23, patient should be on 10 mg for > 3 months
- Film coated formulation different than 5 and 10 mg tablets
- Swallow whole with water
- Do not crush or chew
  - Will increase rate of absorption

Rivastigmine Tartrate (Exelon®) Approved 2000

- Centrally acting and centrally selective pseudo-irreversible AChEI of the carbamate type
  - Prolonged inhibition of AChE > 10 hours
- Indication: Tx of mild to moderate dementia of the Alzheimer’s type
Long-Term Rivastigmine Treatment in Mild to Moderate AD

Results: Cognitive — ADAS-cog

<table>
<thead>
<tr>
<th>Rivastigmine 1-4 mg</th>
<th>Rivastigmine 6-12 mg</th>
<th>Placebo</th>
<th>Projected Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Week</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rivastigmine 1-4 mg</td>
<td>n=191</td>
<td>190</td>
<td>186</td>
</tr>
<tr>
<td>Rivastigmine 6-12 mg</td>
<td>n=143</td>
<td>142</td>
<td>140</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=185</td>
<td>181</td>
<td>177</td>
</tr>
</tbody>
</table>

All patients taking rivastigmine

* p <0.05 ITT-OC analysis.


Rivastigmine Adverse Effects

- Discontinuation rate: 15% (5% placebo)
- Gastrointestinal: 50%
  - Nausea & vomiting: 47% vs 13% placebo
    - Incidence highest during titration phase
  - Weight loss: women = 26%; male = 18%
  - Anorexia: 17% vs 3% placebo
  - Higher incidence than Donepezil
- Relatively devoid of cardiac & hepatic toxicity

Rivastigmine Pharmacokinetics

- Eliminated renally
- Rapidly converted at the site of action in the CNS by cholinesterases via hydrolysis to the decarbamylated metabolite ZNS 114-666
  - T1/2 = 2 hours
  - Metabolized by N-demethylation or sulfate conjugation and eliminated renally
- Not involved with CYP 450 enzyme system
- Smoking may decrease levels by 25%
Rivastigmine Dosing Guidelines
All capsule dosage forms ~$4 (~$8/day)
- 1.5 mg bid for at least 2 weeks
- 3 mg bid for at least 2 weeks
- 4.5 mg bid for at least 2 weeks
- 6 mg bid: Max dose is 12 mg/day
- Dose in AM and PM – q12h with food
- If ADRs occur, D/C for several doses
- If Tx interrupted by days, restart at lowest dose
- May use antiemetics for GI ADEs

Rivastigmine Transdermal Patch
~$8-9/patch
- 4.6 mg/24 hours
  - May increase after 4 weeks to 9.5 mg/24 hours
  - 9.5 mg/24 hours is recommended and maximum dose
- Apply 1 patch daily
- Apply to upper arm or chest or lower/upper back
- Patches cannot be cut; avoid sauna, excessive light
- 129 overdoses & 2 fatal: failure to remove old patch
  - Respiratory depression, seizures, HTN, bradycardia, NVD, salivation, sweating, syncope

Galantamine Hydrobromide
(Razadyne®)
- Approved February 28, 2001
- Extracted from daffodil bulbs
- Competitive and reversible inhibitor of AChE
- Indication: Tx of mild to moderate dementia of the Alzheimer’s type
**Look-Alike/Sound-Alike Errors**

- Reminyl and Amaryl® dispensing errors
- July 2005 name change to Razadyne
- Razadyne and Rozerem® (Ramelteon) 8 mg HS for insomnia
- Aricept and AcipHex® or Ascriptin® or Azilect®

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**Galantamine 5 Month Trial: ADAS-cog Results**

![Graph showing ADAS-cog results for Galantamine (Razadyne)](image)

- Mean change from baseline in ADAS-cog score
- Improvement and Deterioration over 5 months
- Placebo (n = 225)
- REMINYL® 16 mg/d (n = 208)
- REMINYL® 24 mg/d (n = 211)

*P < .001 vs placebo; †P < .001 vs baseline.


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**Galantamine (Razadyne)**

- T1/2 = 7 hours
- F = 90%
  - Food delays Tmax, decreases Cmax 25%
  - No change on AUC
- Metabolized by CYP450 2D6 and 3A4
  - Excreted unchanged in the urine (30%)
  - 2D6 poor metabolizers have a 35% AUC increase
  - Does not induce or inhibit CYP450 system
Galantamine (Razadyne)
All dosage regimens ~$7/day

- ADRs: Nausea, vomiting, diarrhea, anorexia, weight decrease
- Discontinuation 7% with 16 mg/day
- Discontinuation 10% with 24 mg/day
- Dose: 4 mg bid, increased after 4 weeks to 8 mg bid, may increase to 12 mg bid
  - Doses above 24 mg yield limited added benefit
- Renal and hepatic impairment
  - >16 mg should not be exceeded

Razadyne (Galantamine) ER
8 mg, 16 mg, 24 mg (dosed once daily)

Improved Behavioral Effects of Cholinesterase Inhibitors

- Decreased apathy
- Decreased psychosis
- Decreased anxiety, depression
- Decreased agitation
  - Occasional increase in agitation
- Role in non-AD disorders
  - Lewy body dementia
- Synergy with psychotropics
Cholinesterase Inhibitor Relative Contraindications or Warnings

- IBD – diarrhea
- Nausea and vomiting
- PUD – increase gastric acid secretion
- Bladder outflow obstruction
- Bradycardia and Heart Block (SSS)
- Asthma and COPD
- Epilepsy and seizures

Which of the following can decrease the pharmacologic effects and benefits of Rivastigmine in AD?

A. Metoclopramide
B. Diphenhydramine
C. Bethanechol
D. All of the above

Pharmacodynamic Drug Interactions With Cholinesterase Inhibitors

- **Anticholinergics**
  - TCAs, Psychotropics
  - Atropine
  - Scopolamine
  - Cyclopentolate
  - Tropicamide
  - Tolterodine
  - Oxybutynin
  - Dicyclomine
  - Flavoxxate

- **Cholinergics**
  - Neostigmine SC, IM
  - NMBs
  - Succinylocholine

- Metoclopramide
- Diphenhydramine
- Clemastine
- Triprolidine
- Bethanechol
- Minimal CNS effects
Memantine (Namenda™)

Glutamate in the CNS
- Primary ubiquitous CNS excitatory neuron
- Involved in learning, memory, shaping neuronal architecture
- Normalize glutamatergic neurotransmission to maintain or improve cognition, and prevent neurotoxicity
- N-methyl-D-aspartate (NMDA) receptor antagonists

Memantine Selectively Blocks Pathological Activation of NMDA Receptors

Pathological activation of NMDA receptors
Neuroprotection by memantine
Memantine does not impair neurotransmission or plastic processes

Results Global: CIBIC-Plus
Cognition, function, and behavior

The Memantine Group Demonstrated Significantly
Less Global Deterioration Versus Placebo at Week 28

<table>
<thead>
<tr>
<th>Memantine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6</td>
<td>3.8</td>
</tr>
<tr>
<td>4.0</td>
<td>4.2</td>
</tr>
<tr>
<td>4.4</td>
<td>4.6</td>
</tr>
<tr>
<td>4.8</td>
<td>5.0</td>
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</tbody>
</table>

*P=.03 ITT-OC analysis.
†P=.06 LOCF analysis.


Memantine + Donepezil

- Phase 3, multicenter, US, randomized, double-blind, placebo-controlled study
- 404 outpatients with moderate-to-severe AD on stable donepezil
  - MMSE range 5 – 14
- Memantine 10 mg bid
- 5 mg, 10 mg, 15 mg, 20 mg
- 24 weeks duration

Results Functional: ADCS-ADL19
(Modified 19 Item)

| Memantine + Donepezil Preserves Function Significantly Better Than Donepezil Alone |
|---------------------------------|---------------------------------|
| Placebo/donepezil               | Memantine + donepezil            |
| End Point                       |                                 |
| p=0.028                         | p=0.022                         |
| p=0.072                         | p=0.067                         |
| p=0.028                         |                                 |

*P=.028 LOCF analysis.
**Results Cognitive: SIB**

Memantine + Donepezil Produces Sustained Improvement in Cognition Above Baseline Compared With Donepezil Alone

![Graph showing change from baseline SIB score over treatment weeks.](image)

*P<.001 LOCF analysis.

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**Memantine (Namenda™) Pharmacokinetics**

- F = 100%
- T1/2 = 60 - 80 hours
- Linear Pharmacokinetics
- Eliminated renally unchanged
  - May interact with other drugs undergoing tubular secretion
    - Amantadine, cimetidine, ranitidine
- Minimal hepatic metabolism to inactive metabolites
- Does not effect the CYP450 system

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**Memantine (Namenda™) Dosing**

- Clinically effective dose is 20 mg/day
  - Given as 10 mg bid
- Titration schedule
  - Week 1: 5 mg q am
  - Week 2: 5 mg bid
  - Week 3: 10 mg q am and 5 mg hs
  - Week 4: 10 mg bid
- No food effect
**Ginkgo Biloba**
- Placebo controlled trials show mild benefit in cognitive function with 3 – 6 months of treatment
- Dosage: 120 – 240 mg daily
- No standard form available
- Increased risk of hemorrhage
  - Inhibits platelet aggregation
  - Recent 6-week trial showed no improvement in cognition


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**Conclusions**
- Treatment can slow disease progression, slow loss of cognitive and functional abilities and ameliorate behavioral symptoms
- Donepezil is the best tolerated Cholinesterase Inhibitor, it is administered once daily, and has an easy titration schedule
- Pharmacotherapy requires a cocktail approach
  - Cholinesterase Inhibitors
  - Memantine
  - Vitamin E 1,000 Units bid (?)

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**Questions**

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**Thanks!**