Medical Treatment of Alzheimer’s disease

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Pathophysiology

• Amyloid hypothesis
  – Amyloid precursor protein
  – BACE 1, gamma secretase
  – Beta amyloid: multible form
    • Soluble oligomers /intermediate myloids (most neurotoxic form)
    • Fibrils >> beta amyloid plaque
Pathophysiology

- **TAU**
  - Soluble, promote stability of microtubules and vesicle transport
  - Hyperphosphorylated tau is insoluble, lacks affinity of microtubules
  - Self associates into paired helical filament
  - Neurofibrillary tangles
  - Cytotoxic / impaired cognition
tau

Hyperphosphorylation of tau

Microtubule

Destabilized microtubules

Neurofibrillary tangles
Neurotrophin and neurotransmitter

• Neurotrophins promote proliferation, differentiation, and survival of neurons and and they mediate learning, memory, and behavior

• In AD, beta amyloid binds to brain-derived neurotrophic factor (BDNF) receptor (a member of the neurotrophin family) >> BDNF suppression

• Aβ binds to α-7 nicotinic acetylcholine receptors, impairing the release of Ach.

• Level of muscarinic acetylcholine receptors is reduced
Neuronal excitotoxicity

Excitatory neurotransmitter glutamate receptor (NMDA receptor)

High level of Ca ions enter cell

Activated enzyme (phospholipase, endonuclease, protease)

Cell damage
Medical treatment

• Goal
  – temporary improvement, stabilization, or less than-expected decline of cognitive, functional, and behavioral symptoms.

• Cognition and ADL
  – Cholinesterase inhibitor
  – N-methyl- D- aspartate receptor antagonist
  – Alternative medicine

• Neuropsychiatric symptom
<table>
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<tr>
<th>Medication</th>
<th>Dose</th>
<th>Common Adverse Side Effects</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td>5 mg/day at bedtime with or without food for 4 to 6 weeks; 10 mg/day there-after, if tolerated</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams</td>
<td>Available in a single daily dose</td>
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<tr>
<td>Rivastigmine (Exelon)</td>
<td>3 mg daily, split into morning and evening doses with meals; dose increased by 3 mg/day every 4 weeks as tolerated, with a maximum daily dose of 12 mg</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, indigestion, dizziness, drowsiness, headache, diaphoresis, weakness</td>
<td>Available as a patch</td>
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<tr>
<td>Galantamine (Razadyne)</td>
<td>8 mg daily, split into morning and evening doses with meals; dose increased by 4 mg every 4 weeks, as tolerated, with a maximum daily dose of 16 to 24 mg</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, headache, fatigue</td>
<td>Available as an extended-release capsule</td>
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<tr>
<td>Memantine (Namenda)</td>
<td>5 mg/day with or without food; dose increased by 5 mg every week, with a maximum daily dose of 20 mg</td>
<td>Constipation, dizziness, headache, pain (nonspecific)</td>
<td>Often used as an adjunct to cholinesterase inhibitors; not recommended alone for treatment of early disease</td>
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rivastigmine
Cholinesterase inhibitor

- RCT of cholinesterase inhibitors have included mainly mild-to-moderate AD patient and have shown significant benefits with respect to cognition, daily function, and behavior.

- The condition of patients remains stable for a year or more and then may decline, though at a rate that is slower than untreated patients.
Cholinesterase inhibitor

• Result improvement of 2 to 3 points on the Alzheimer’s Disease Assessment Scale for cognition (scale 0 to 70, with higher scores indicating better cognition)
• a decreased rate of decline, as compared with the placebo group (3 point difference)
• No significant differences in effects on cognitive performance among three cholinesterase inhibitors during the study period (usually, 3 to 6 months)

(systematic review and meta-analysis of data from 27 randomized trials)
Alzheimer’s Disease Assessment Scale for cognition

- spoken language ability (0-5),
- comprehension of spoken language (0-5),
- recall of test instructions (0-5),
- word finding difficulty (0-5),
- following commands (0-5),
- naming object (0-5),
- Construction drawing (0-5),
- ideational praxis (0-5),
- orientation (0-8),
- word recall (0-10),
- word recognition (0-12).

- ranges from 0-70, the high score indicating greater impairment.
Cholinesterase inhibitor

• Daily function : On the basis of 14 studie, donepezil was modestly but significantly more effective than rivastigmine.

• Behavior (as measured by the NPI) : Donepezil was likewise modestly but significantly better than rivastigmine and galantamine.

4.3 point reduction of donepezil VS 1.4 point reduction of other agent
Table 2  Clinical Benefits of Cholinesterase Inhibitors in Patients with Alzheimer’s Disease

<table>
<thead>
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<th>Benefit</th>
<th>Description</th>
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<tbody>
<tr>
<td>Improve, or delay, the decline of cognition</td>
<td>21- to 26-week trials showed statistically significant benefits in ADAS-cog and MMSE&lt;sup&gt;10,19-24&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cognitive benefits sustained over 3 to 5 years&lt;sup&gt;9-11,25,26&lt;/sup&gt; compared with projected rates of decline expected of untreated patients with Alzheimer’s disease</td>
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<tr>
<td>Improve global function</td>
<td>24- to 26-week trials showed improvement in about 20% to 40% of patients&lt;sup&gt;10,19,20,22-24&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>21- to 26-week trials showed stabilization/improvement in 64-70% of patients&lt;sup&gt;10,21,22&lt;/sup&gt;</td>
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<tr>
<td>Preserve functional ability</td>
<td>Reduce the decline in basic and instrumental activities of daily living over treatment periods of 6 months to at least 1 year&lt;sup&gt;10,19,22,25&lt;/sup&gt;</td>
</tr>
<tr>
<td>Improve disturbed behaviors or reduce the emergence of new behavioral symptoms&lt;sup&gt;21,27-29&lt;/sup&gt;</td>
<td>May reduce need for psychotropic medications&lt;sup&gt;29&lt;/sup&gt;</td>
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<tr>
<td>Reduce caregiver burden&lt;sup&gt;30,31&lt;/sup&gt;</td>
<td>Delay nursing home placement&lt;sup&gt;32-34&lt;/sup&gt;</td>
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<tr>
<td>Pharmacoeconomic benefits demonstrated&lt;sup&gt;34&lt;/sup&gt;</td>
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Side effect

• nausea, vomiting, diarrhea, dizziness, and weight loss were frequent with all three medications, although slightly less frequent with donepezil than with the other drug

• Drug interaction
  – Donepezil , galantamine : cytochrome P450
  – Rivastigmine : brain esterase
Memantine

• An $N$–methyld-$D$-aspartate antagonist
• Moderate to severe Alzheimer’s disease,
  – interfere with glutamatergic excitotoxicity
  – symptomatic improvement through effects on the function of hippocampal neurons.
• significant reduction in cognitive deterioration
Memantine

- mild or early-stage disease have shown no significant benefit of memantine therapy.

- Memantine has also been used in patients with late-stage disease in combination with cholinesterase inhibitors with modest improvement (a relative change in score of 2-5 %)
Timing

• When to start treatment
  – MCI: positive trial of donepezil
    negative trial of galantamine (cochrane systematic review)
  – patients who were treated early in the disease course had improvement that was only slightly greater than that of patients who began treatment later
Withdrawal of treatment

• If a patient deteriorates to the point that there is dependency in all BADL, meaningful social interactions and quality of life benefits are no longer possible, pharmacologic treatment should be withdrawn.

• Deterioration in cognition, function, or behavior during withdrawal may indicate a continuing response and may suggest the agent should be continued.
Medical treatment

• A rational approach is to try a cholinesterase inhibitor first, switching to another agent in the same class if the initial agent is ineffective or if intolerable side effects emerge. (optimal dosage?)

• Memantine may be added to any of the cholinesterase inhibitors in patients who have little or no improvement with cholinesterase inhibitor monotherapy.
Mild to moderately AD

FIRST-LINE CHOLINESTERASE INHIBITOR THERAPY
Rivastigmine or Donepezil or Galantamine
Titrated to maximally tolerated dose within therapeutic range

Treatment failure/loss of clinical benefits/intolerance

Yes

Switch to another cholinesterase inhibitor:
- Donepezil to Rivastigmine, or alternatively, Galantamine
- Rivastigmine to Galantamine, or alternatively, Donepezil
- Galantamine to Rivastigmine, or alternatively, Donepezil

Inadequate or poor clinical response to Cholinesterase Inhibitor monotherapy

Addition of Memantine may be considered in moderate AD
Not FDA approved for this indication

Inadequate or poor clinical response to all Cholinesterase Inhibitors

Substitution of Memantine may be considered in moderate AD

Treatment failure/loss of clinical benefits/intolerance

Yes

Withdrawal of Cholinesterase Inhibitor and/or Memantine

No

Maintain on therapy and monitor
Moderate to Severe AD or previous treatment of AD

FIRST-LINE THERAPY
NMDA Antagonism with Memantine
Titrate to target dose

Are there acceptable clinical benefits: stabilization and/or improvements in cognitive, functional behavioral impairments?

No
Yes

Maintain on therapy and monitor

Consider combination therapy for patients with poor response to memantine
Memantine + a Cholinesterase Inhibitor
Note that cholinesterase inhibitors are currently not FDA-approved for patients with severe AD

Does the patient manifest behavioral disturbances of severe AD?
Treatment triggers include aggression, psychosis, hallucinations, paranoia, delusions, delirium

Yes
No

Maintain on therapy and monitor

Agents that may be considered for management of behavioral disturbances include atypical antipsychotics, anticonvulsants, anti-depressants

Clinical judgment and ongoing clinical assessment will determine optimal drug selection and modification approaches -- titration, switching, adding, withdrawal -- for the individual patient

Treatment failure/lack of clinical benefits despite maximization of medical therapy

Yes
No

Maintain on therapy and monitor

Withdrawal of Cholinesterase Inhibitor and/or Memantine therapy
Antiamyloid therapy

• No antiamyloid therapies are currently available.

• Antiamyloid vaccination program was interrupted with encephalitis develop in 6 %. F/U no cognitive or survival benefit despite diminution of plaque

• Ongoing clinical studies
  – passive and active amyloid immunisation
  – Gamma secretase inhibitor
Ongoing study

- Agent that inhibit tau oxidation and aggregation (methylene blue)
- BDNF treatment in non human primate support neuronal survival, synaptic function, memory
Ginkgo biloba

- effects on cerebral blood flow
- neurotransmitter systems
- cellular redox state
- nitric oxide levels
- antagonism of platelet activating factors
- Some recent studies also suggest a direct role in modulating amyloid aggregation and pathology.
Ginkgo biloba

- Although pooling several small trials of Ginkgo extract suggested a modest benefit (small, short duration)
- The recently published large, well-designed, clinical trial that showed no overall benefit
Antioxidant: vitamin E

• The conclusion of a Cochrane database systematic review 2008 is that there is insufficient evidence for the efficacy of vitamin E in the treatment of AD or MCI.
Antiinflammatory agent

• The brain of patients with AD have microscopic evidence of inflammation.
• Observational trials of prednisolone, diclofenac, naproxen, rofecoxib are negative.
Hormone replacement

- randomized, placebo-controlled trials of estrogen-replacement therapy in postmenopausal women showed no benefit.
- The Women’s Health Initiative study of estrogen plus medroxyprogesterone acetate showed an increased risk of dementia among postmenopausal women.
Psychiatric symptom

• Depression and anxiety are frequent even in the early stage of AD.
  – SSRI are commonly used
  – Tricyclic antidepressants are generally avoided, since their anticholinergic effects can cause or exacerbate confusion
Psychiatric symptom

• Psychosis: delusion, hallucination
  – Conventional or atypical antipsychotic agent

• Causion of parkinsonism, extrapyramidal signs, sedation, confusion