Pharmacologic Treatment of Dementia

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Overview of Dementias

The common dementias
- Alzheimer dementia (AD)
- Dementias with Lewy bodies (DLB)
- Vascular dementia (VaD)
- Frontotemporal dementia (FTD)
Current State of Treatment

Largely driven by Alzheimer disease
No cures (not even close)
Some possible preventive strategies
Nothing new for about 10 years
- Treatments focus on cognitive symptoms

Cholinesterase Inhibitors

AcetylCholine deficit in AD
- Diminished ACh in cerebral cortex
- Cholinergic cell loss in nucleus basalis

AcetylCholinesterase (AChE) destroys ACh
- Block AChE
- Increase levels of ACh
Cholinesterase Inhibitors

Donepezil (*Aricept*)
- Mild, moderate, severe AD
- Tablet, XR tablet, disintegrating tablet (ODT)

Rivastigmine (*Exelon*)
- Mild, moderate, severe AD and PDD
- Capsule, liquid, XR transdermal patch

Galantamine (*Razadyne*)
- Mild, moderate AD
- Tablet, liquid, XR capsule

AChe-I Side Effects

Cholinergic
- GI upset
- Bradycardia
- Increased respiratory secretions

Other
- Decreased appetite and weight loss
- Drowsiness or insomnia
- Adverse behavioral changes
- Nightmares
Evidence of Efficacy is Based on Clinical Trials

Alzheimer's Disease
- Cognition
- Global well-being
- Basic activities
- Behavior

Clinical Trial
- ADAS, NTB, SIB
- CDR, CIBIC+
- ADCS ADL
- NPI

Provider's Office
- MMSE, MoCA
- How is s/he doing?
- What can s/he do at home?
- How is mood, activity level, etc

ADAS – AD Assessment Scale; ADCS – Alzheimer Disease Cooperative Study; ADL – activities of daily living; CDR – Clinical Dementia Rating; CIBIC – Clinician Interview Based Impression of Change; NPI – Neuropsychiatric Inventory; NTB – Neuropsychological Test Battery; SIB – Severe Impairment Battery

Rivastigmine & ADAS-Cog

Double Blind placebo
- Rivastigmine
- Placebo

All active
- Rivastigmine
- Placebo

Mean ΔADAS-Cog

Weeks

0 12 18 26 38 44 52

+P < 0.001 vs placebo
†P < 0.05 vs placebo
Observed case analysis

**Galantamine & MMSE**

- Mean Δ ADAS-Cog
- Double Blind Placebo
- Open, Active

- 24 mg
- 32 → 24 mg
- Placebo → 24 mg

**Donepezil & CIBIC*-plus**

- CIBIC-plus Score
- Mean Score ± SE
- Weeks
- Donepezil
- Placebo

*Clinician interview based impression of change

 Donepezil  n=133→120
 Placebo  n=137→126
Galantamine & CIBIC-plus
Six Months

Placebo  Galantamine 24 mg  Galantamine 32 mg

P = .002  P < .001

Patients (%)

Mod improved  Min improved  No change  Min worse  Mod worse  Mark worse

Effects on ADLs

Rivastigmine

Galantamine

Placebo  Low (8 mg)  High (16 mg)

Placebo  Low (8 mg)  Med (16 mg)  High (24 mg)

Donepezil & Behavior

![Graph showing NPI total score improvement and decline over weeks for Donepezil and Placebo groups.](image)

- **Donepezil (n=138→119)**
- **Placebo (n=144→125)**

**Weeks:**
- 0
- 2
- 4
- 8
- 12
- 18
- 24

**Improvement:**
- p=0.0303
- p=0.0618
- p=0.0083
- p=0.0005

**Decline:**

- ΔNPI total score:
  - -8
  - -6
  - -4
  - -2
  - 0
  - 2
  - 4

- Weeks:
  - 4
  - 8
  - 12
  - 18
  - 24

- LOCF

**Clinical Improvement:**

- Persistent donepezil
- Placebo

**Clinical Decline:**

- Open-label (n=128)
- Double-blind (n=96)

- *P<0.0001 vs baseline
- †P<0.05 Aricept vs placebo

Donepezil & NPI Sub-scores

**p<0.05**

-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0

Donepezil
Placebo

∆ NPI Score at Week 24 [MMSE]

- Delusions
- Hallucinations
- Agitation
- Depression
- Anxiety
- Elation
- Apathy
- Disinhibition
- Irritability
- Aberrant motor behavior
- Night-time behaviors
- Appetite/eating

Improvement
Decline

Probability of Remaining at Home

- < 80 mg/day
- 80-120 mg/day
- 120-160 mg/day

Knopman et al., Neurology, 1996

Tacrine and Remaining at Home
**AChE-I Summary**

AChE-I stabilize cognitive status
- Effect lasts for at least six months
- Starting earlier leads to better outcomes

AChE-I may help with behavior
- Largest effect on apathy
- Some benefit in depression and anxiety

AChE-I do not affect underlying disease
- Cognitive decline continues
- Discontinuation reverses effects

**NMDA Receptor Antagonist**

Memantine (*Namenda*)
- FDA approved for moderate, severe AD
- Tablets

Side effects
- Headache
- Drowsiness
- Dizziness
- Adverse behavioral changes
Memantine Add-on Treatment: Severe Impairment Battery (SIB):


Placebo + Donepezil (n=197→153)
Memantine + Donepezil (n=198→171)

Guidelines for Use

Data support early treatment at high dose
Minimal evidence for AChE-I efficacy in MCI
Minimal evidence for memantine efficacy in MCI or early AD
Studies of switching AChE-I not well regarded
Combining memantine and AChE-I safe
Non-AD Dementias

Vascular dementia
- Mixed data, most support AchE-I

Frontotemporal dementia
- No evidence of cholinergic deficit
- AChE-I can cause behavioral worsening
- Memantine may stabilize behavior (not cognition)

Non-AD Dementias

Lewy body dementias (DLB and PDD)
- Severe cholinergic deficit
- Significant burden of other symptoms (hallucinations, Parkinsonism)
- AChE-I slow progression of symptoms
- AChE-I particularly beneficial for hallucinations
- Memantine improves quality of life
Future Directions

Optimization of current therapies

Disease-modifying therapies
- Pre-symptomatic diagnosis with amyloid PET
- Reduce impact of amyloid/tau accumulation

Prevention through lifestyle changes
- Abundant retrospective evidence for vascular protection
- Prospective studies needed

Gene treatment
- Small minority of cases