TREATMENT OF ALZHEIMER’S DISEASE
**Central Cholinergic Synapse**

- **Acetyl CoA + Choline**
- **Cholinesterase Inhibitors**
  - (-) M2 Muscarinic 1 receptor
  - (+) Muscarinic 1 receptor

**Cholinesterase Inhibitors**
- Choline + Acetate

**Post synaptic**
- **Muscarinic 1 receptor**
Treatment Imperatives at the Various Stages of Disease Progression

- Expectations should center on slowing decline or delaying institutionalization rather than overall cure or significant improvement.

- Modest improvements are temporarily appreciable in at best 30% of patients with currently available symptomatic therapies.

- Current treatments for Alzheimer’s disease may delay symptomatic decline of the disease; they cannot be considered to affect the biological disease process or to be disease-modifying.

- A disease-modifying therapy delaying the onset of Alzheimer’s disease by 5 years will reduce its overall prevalence by 50%; a delay of 10 years will produce a 75% reduction.

ALZHEIMER DISEASE: PHARMACOLOGICAL APPROACHES

Acetylcholine

*ChE inhibitors*
Muscarinic or nicotinic agonists

β-amyloid

Alter APP formation
Block β-amyloid formation
Inhibit β-amyloid aggregation
Immunization

Estrogen
Antioxidants
NSAIDs
Cell cycle inhibitors

Glutamate
Memantine
AchE inhibitors in mild to moderate Alzheimer's disease
Cholinesterase inhibitors: a rational therapeutic approach in AD

- **Tacrine**
  - Mechanism: AChE/BuChE-I
  - Inhibition: reversible

- **Donepezil**
  - Mechanism: AChE-I
  - Inhibition: reversible

- **Galantamine**
  - Mechanism: AChE-I
  - Inhibition: reversible

- **Physostigmine**
  - Mechanism: AChE/BuChE-I
  - Inhibition: pseudo-irreversible

- **Rivastigmine**
  - Mechanism: AChE/BuChE-I
  - Inhibition: pseudo-irreversible

- **Metrifonate**
  - Mechanism: AChE/BuChE-I
  - Inhibition: irreversible

Weinstock, 1999
Acetylcholine Synapse: Site of Cholinesterase Inhibitor Action

Adapted with permission from Adem A. Acta Neurol Scand Suppl. 1992;139:69-74.
Both AChE and BuChE break down ACh in the brain

1. Electrical impulse triggers ACh release
2. ACh diffuses towards ACh receptors on the post-synaptic neuron
3. AChE + BuChE hydrolyse ACh
4. ACh $\Rightarrow$ acetic acid + choline
5. Return to the pre-synaptic neuron, regenerating ACh

AChE=acetylcholinesterase
BuChE=butyrylcholinesterase
Butyrylcholinesterase (BuChE)

- BuChE and acetylcholinesterase (AChE) are members of the same family of enzymes
- Both AChE and BuChE regulate the neurotransmitter acetylcholine (ACh) in the brain
- Likely to play a key role (rather than just a back-up role) in improving cholinergic neurotransmission

Mesulam et al. 2002; Darvesh et al. 2003
Distribution of cholinesterases in the healthy human brain

- AChE neurons are abundant in the brain
- BuChE is rich in limbic areas (amygdala, hippocampus and thalamus)

Darvesh et al. 1998

Mesulam, 2000
Distribution of cholinesterases in the healthy human brain
BuChE activity increases in the AD brain
AChE activity decreases and relative BuChE activity increases in the AD brain.

Arendt et al. 1992
AChE activity decreases and BuChE activity increases with disease progression

- BuChE activity increases by 40-90% as the disease progresses, while AChE activity decreases by 45%\(^1\)

Perry et al. 1978
BuChE activity increases in the AD brain, compared with healthy controls

BuChE staining in the temporal cortex of a 71 year-old patient with AD. BuChE is found in plaques (←), tangles (← ), dystrophic neurites (← ), and glia (→)

BuChE staining in an 89 year-old non-demented individual. BuChE staining is limited to the glia (→)

Guillozet et al. 1997
Relation between ChE activity and numbers of senile plaques in the cerebral cortex

ChE = cholinesterase

Perry et al. 1978b
Dementia patients with 'less active' BuChE (e.g. k-variant) have slower disease progression.

Annual change in CAMCOG score

Wild-type BuChE (n=19)  K-variant BuChE (n=6)

p=0.04

CAMCOG=Cambridge Cognitive Examination

*Moderate to severe patients diagnosed with DLB or AD

O’Brien et al. 2003
Activity of BuChE and $\text{A}\beta$ deposition in AD cortex

Cerebral BuChE activity (nmol x min$^{-1}$ x mg$^{-1}$ protein)

Density of Ab deposition in neocortical area 8 (mm$^{-3}$)

$r=0.86$

Arendt et al. 1992
Inhibition of either AChE or BuChE in the brain increases ACh concentration

*Preclinical studies

Giacobini et al. 1996
AChE or BuChE specific inhibitors improve cognitive performance of elderly rats

Maze

Food

Mean errors per trial

- Control
- 0.25 mg/kg
- 0.5 mg/kg
- 1 mg/kg

AChE inhibition (Phenserine)
BuChE inhibition (Bisnorcymserine)

Greig et al. 2001
# Drug treatments for AD

**Table 1. Clinical Pharmacology of Agents Useful for Reducing the Signs of Dementia.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donepezil (Aricept)</th>
<th>Rivastigmine (Exelon)</th>
<th>Galantamine (Reminyl)</th>
<th>Memantine (Namenda)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to maximal serum concentration (hr)</td>
<td>3–5</td>
<td>0.5–2</td>
<td>0.5–1</td>
<td>3–7</td>
</tr>
<tr>
<td>Absorption affected by food</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Serum half-life (hr)</td>
<td>70–80</td>
<td>2†</td>
<td>5–7</td>
<td>60–80</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>96</td>
<td>40</td>
<td>0–20</td>
<td>45</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP2D6, CYP3A4</td>
<td>Nonhepatic</td>
<td>CYP2D6, CYP3A4</td>
<td>Nonhepatic</td>
</tr>
<tr>
<td>Dose (initial/maximal)</td>
<td>5 mg daily/10 mg daily</td>
<td>1.5 mg twice daily/6 mg twice daily</td>
<td>4 mg twice daily/12 mg twice daily</td>
<td>5 mg daily/10 mg twice daily</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Cholinesterase inhibitor</td>
<td>Cholinesterase inhibitor</td>
<td>Cholinesterase inhibitor</td>
<td>NMDA-receptor antagonist</td>
</tr>
</tbody>
</table>

* CYP2D6 denotes cytochrome P-450 enzyme 2D6, CYP3A4 cytochrome P-450 enzyme 3A4, and NMDA N-methyl-D-aspartate.
† Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has an eight-hour half-life for the inhibition of acetylcholinesterase in the brain.
AD: Many patients treated for a short time, relative to long-term duration of disease

- AD persists on average for 7–10 years
- In general, patients are treated with cholinesterase (ChE) inhibitors for only a short duration (e.g. <200 days in the US)

Brookmeyer et al. 2002
### ChE inhibitors: Different pharmacological characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivastigmine</th>
<th>Donepezil</th>
<th>Galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme(s) inhibited</td>
<td>AChE and BuChE</td>
<td>AChE</td>
<td>AChE</td>
</tr>
<tr>
<td>Sustained ChE inhibition after long-term treatment</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>nAChR modulation?</td>
<td>No</td>
<td>No (?)</td>
<td>Yes</td>
</tr>
<tr>
<td>Plasma half-life (hours)</td>
<td>1–2</td>
<td>~70</td>
<td>~6</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Very slowly reversible</td>
<td>Reversible</td>
<td>Reversible</td>
</tr>
</tbody>
</table>

Sifton (Physician’s Desk Reference), 2002; Svensson, 1997; Weinstock, 1999; Samochocki et al. 2000; Amici et al. 2001; Davidsson et al. 2001; Darreh-Shori et al. 2002; Parnetti et al. 2002
Potential benefits of inhibiting both AChE and BuChE

Dual inhibition

Improved cholinergic transmission
Possible effect on Aβ

Which translates into broader and more sustained efficacy:

- Attention, cognition and behaviour
- Quality of life
- Autonomy
- Disease progression?
Treatment of Alzheimer's Disease

* Any drug treatment, not limited to acetylcholinesterase inhibitors.

Dual inhibition of AChE and BuChE

- Sustained inhibition of both AChE and BuChE is correlated with clinical benefit
- Additional inhibition of BuChE may have disease-modifying effects
- AChE and BuChE inhibition versus AChE-specific inhibition currently being studied
Benefits of Treatment of AD With Acetylcholinesterase Inhibitors

- AChEIs may improve, maintain, or slow the decline of cognitive, behavioral, and functional performance in patients with mild-to-moderate AD.

- Delay of treatment leads to loss of potential benefit.

- AChEIs may delay nursing home placement over 20 months, and potentially much more when started early.

- AChEIs have demonstrated consistent efficacy and safety in maintaining cognitive function, as measured by ADAS-cog in patients with mild-to-moderate AD for up to 1 year - relative to placebo!!
  - Donepezil\(^1\) 38 weeks
  - Rivastigmine\(^2\) 38–42 weeks
  - Galantamine\(^3\) 52 weeks (25–30% better)

Selective BuChE inhibition reduces APP and Ab levels

PEC = (-)-Phenethylcymserine
APP = amyloid precursor protein

Data courtesy of N. Greig
Both AChE and BuChE inhibition reduces APP levels in transgenic mice

Borchelt et al. 1996

*p<0.05 vs control
<table>
<thead>
<tr>
<th>Type and Drug</th>
<th>Initial Daily Dose</th>
<th>Final Daily Dose (Range)</th>
<th>Targeted Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5 mg daily</td>
<td>1.0 mg (0.75–1.5 mg daily)</td>
<td>Psychosis and agitation</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5 mg daily</td>
<td>5.0 mg (5–10 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25 mg daily</td>
<td>200 mg (50–150 mg twice day)</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20 mg daily</td>
<td>40 mg (20–80 mg twice a day)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10 mg daily</td>
<td>10 mg (10–30 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Neureptic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.25 mg daily</td>
<td>2 mg (1–3 mg daily)</td>
<td>Psychosis and agitation</td>
</tr>
<tr>
<td>Mood stabilizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>125 mg twice a day</td>
<td>500 mg (250–500 mg twice a day)</td>
<td>Agitation</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200 mg twice a day</td>
<td>400 mg (200–500 mg twice a day)</td>
<td></td>
</tr>
<tr>
<td>Selective serotonin-reuptake inhibitor</td>
<td></td>
<td></td>
<td>Depression, anxiety, psychosis, and agitation</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10 mg daily</td>
<td>20 mg (20–40 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5 mg daily</td>
<td>10 mg (10–20 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 mg daily</td>
<td>20 mg (10–40 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>25 mg daily</td>
<td>75 mg (75–100 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5 mg daily</td>
<td>10 mg (10–40 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td></td>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td>Nortriptiline</td>
<td>10 mg daily</td>
<td>50 mg (25–100 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>10 mg daily</td>
<td>100 mg (50–200 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Serotonin- and noradrenergic-reuptake inhibitor</td>
<td></td>
<td></td>
<td>Depression and anxiety</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>25 mg twice a day</td>
<td>200 mg (100–150 mg twice a day)</td>
<td></td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressant</td>
<td></td>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7.5 mg daily</td>
<td>15 mg (15–30 mg daily)</td>
<td></td>
</tr>
</tbody>
</table>
Exelon Improves Cognitive Function: ADAS-Cog mean change from baseline

†B352 OC study analysis; *p<0.05 vs placebo

Exelon Longterm Effects on Cognition: Mean Change in ADAS-Cog from Baseline at Week 52

Study Week


B352 Patients in B353 (OC) at Week 52
* p< 0.05 vs projected placebo
Rivastigmine: Long-lasting dual inhibition of AChE and BuChE in patients with AD

CSF—closest available marker to brain

Cutler et al. 1998
Long-term effects of rivastigmine on cognition: ADAS-Cog

- Rivastigmine 6–12 mg/day
- Rivastigmine 1–4 mg/day
- Placebo
- Projected placebo

ADAS-Cog mean change (± SEM) from baseline

Study week

- *p<0.001 vs placebo
- **p<0.001 vs projected placebo

Farlow et al. 2000
AD drug sales in the USA
Changes in treatment
ChE inhibitors in the management of behavioural symptoms in dementia

‘Cholinesterase Inhibitors: A new class of psychotropic compounds.’

‘Cholinesterase inhibitors have psychotropic effects and may play an important role in controlling neuropsychiatric and behavioral disturbances in patients with Alzheimer’s disease.’

“and in Dementia with Lewy bodies”
Patients with cognitive decline on donepezil improved/stabilised after switch to rivastigmine.

Mean MMSE score ± SD

- Start of donepezil treatment: 22.5 ± 3.1
- End of donepezil treatment: 19.4 ± 3.1
- Start of rivastigmine treatment (baseline): 18.2 ± 3.1
- After 16 weeks of rivastigmine treatment: 18.5 ± 3.1
- After 26 weeks of rivastigmine treatment: 19.2 ± 3.1

3.1-point deterioration

n=205

*p<0.001 vs. start of donepezil treatment; **p<0.001 vs. baseline

Auriacombe et al. 2003
Efficacy or tolerability issues with donepezil are not predictive of similar problems with rivastigmine.

Response to rivastigmine (GCIC) after lack/loss of efficacy with donepezil (n=304)

Adapted from Auriacombe et al. 2002

Tolerability of rivastigmine after safety/tolerability issues with donepezil (n=78)

Adapted from Auriacombe et al. 2002
Transdermal treatment

- The rivastigmine patch (Exelon®) is the first transdermal treatment for Alzheimer’s disease.

- The therapeutic dosage of 9.5 mg has a similar effect with the dosage of 12 mg and the frequency of nausea and vomiting similar with the placebo drug.

- It is easily applied and does not cause any problems while on the skin.

- Καλύτερα ανεκτό στους ασθενείς από ότι η θεραπεία από του στόματος.
Body Places for the Patch
Long-term Cognitive Benefits of Reminyl® (galantamine HBr) Treatment

![Graph showing cognitive benefits over time](image)

**Mean (± SE) change from baseline in ADAS-cog score**

- **Double-blind**
  - Placebo/Reminyl® 24 mg
  - Reminyl® 24 mg/Reminyl® 24 mg
  - Historical placebo group

- **Open-extension**
  - Placebo/Reminyl® 24 mg
  - Reminyl® 24 mg/Reminyl® 24 mg

- **Improvement**
  - Deterioration

*p < 0.05 vs placebo/Reminyl® (not statistically different from baseline).

Effect of Reminyl® (galantamine HBr) on Behavioral Symptoms: NPI

* Mean (± SE) change from baseline in NPI

- Placebo
- Reminyl® 16 mg/d
- Reminyl® 24 mg/d

Dose increments

Improvement

Deterioration

OC, observed cases.
* Not significant vs baseline.
† p < 0.05 vs placebo (Reminyl® 16 and 24 mg).
‡ p < 0.05 vs baseline.

Adapted with permission from Tariot PN et al. Neurology. 2000;54:2269-2276.
V. ALZHEIMER’S DISEASE TREATMENT

- Non pharmaceutical
  - Cognitive, Behavioural, Nursing
  - Technological
    (Global Positioning System, Robots, Wireless audiovisual networks)
  - Training of caregivers, health professionals
**Funded AD Prevention and Selected Treatment Trials**

- **1998:** Vitamin E, C, B6, B12, Folate, B-Carotene
- **1999:** Vitamins E, Aricept
- **2000:** Aspirin, Vitamin E
- **2001:** Estrogen
- **2002:** B-Carotene, Vit. E, C
- **2003:** Celecoxib, Naproxen
- **2004:** Ginkgo Biloba
- **2005:** Vitamin E, Selenium
- **2006:** Simvastatin
- **2007:**
- **2008:**

*April 2002*
Ευχαριστώ για την προσοχή σας
Ευχαριστώ για την προσοχή σας
Lesson of Byzantine music
Activities of AD patients