Anti-Alzheimer's Drugs

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Cholinesterase Inhibitors

- 4 acetylcholinesterase inhibitors (AChEIs)
  - Tacrine (1993)
  - Donepezil (1996)
  - Rivastigmine (2000)
  - Galantamine (2001)

Cholinergic hypothesis

1: Science. 1982 Jul 30;217(4558):408-14.

The cholinergic hypothesis of geriatric memory dysfunction

- Cholinergic deficits was found in AD brains
  - Degeneration of basal forebrain nuclei
  - Progressive loss of nicotinic receptors in AD
- Cholinergic transmission is important
  - Cognitive, functional, behavioral symptoms
  - Pathological, biochemical, pharmacological basis
- Challenging views
  - ChAT & AChEI do not drop until the later disease stages
  - Cholinergic signal transduction defects may be related in early stages

Mechanism of AChEIs

- **Inhibition of the catalytic enzyme**
  - **Increase the availability of ACh**
- **Neuroprotective effect**
  - **Influence on APP processing and β-amyloid production**
  - **Increase expression of nicotinic receptors**

Mechanisms Behind the Neuroprotective Actions of Cholinesterase Inhibitors in Alzheimer Disease

Agneta Nordberg, MD, PhD

Alzheimer Dis Assoc Disord • Volume 20, Supplement 1, April/June 2006

Clinical efficacy of AChEIs

Cholinesterase inhibitors for Alzheimer's disease (Review)

Birks J

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Cochrane Dementia and Cognitive Improvement Group

(CDCIG)

THE COCHRANE COLLABORATION

Clinical efficacy on cognition

- **Clinical trials showed small but significant benefits**
  - **2.8 - 4.0 point on the 70 point of ADAS-cog over 6 months**
  - **2.7 average points (mild to severe dementia, 10 trials)**
  - **1 - 1.5 point on MMSE over 6 months**

Table 1. ADAS-cog (0-70) weighted mean difference after 6 month's treatment versus placebo

Treatment	Dose (mg)	ADAS-cog WMD (95% CI)
Donepezil	5	-1.85 (-2.6, -1.11)
	10	-2.90(-3.65,-2.15)
Rivastigmine	1-4	-0.84(-1.48,-0.19)
	6-12	-2.09(-2.65,-1.54)
Galantamine	8	-1.30(-2.75,-0.02)
	16	-3.10(-4.12,-2.07)
	24	-3.28(-3.92,-2.65)

(Scarpini E et al., Lancet Neurol 2003)

Clinical efficacy on BPSD

- **Small but statistically significant improvements**
  - **NPI or ADAS-noncog**

Analysis 01.05. Comparison 01 Cholinesterase inhibitor (optimum dose) vs placebo, Outcome 05 Behavioural disturbance (NPI) mean changes from score from baseline at 6 months (ITT)

Review: Cholinesterase inhibitors for Alzheimer's disease

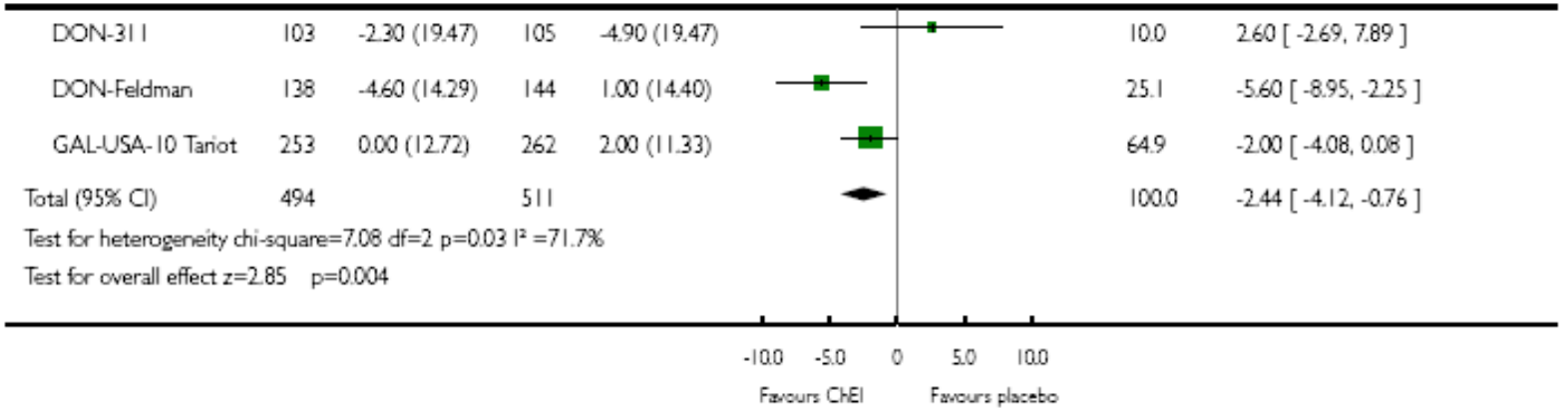
Comparison: 01 Cholinesterase inhibitor (optimum dose) vs placebo

Outcome: 05 Behavioural disturbance (NPI) mean changes from score from baseline at 6 months (ITT)

Study	ChEI		Placebo		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
DON-311	103	-2.30 (19.47)	105	-4.90 (19.47)		10.0	2.60 [-2.69, 7.89]
DON-Feldman	138	-4.60 (14.29)	144	1.00 (14.40)		25.1	-5.60 [-8.95, -2.25]
GAL-USA-10 Tariot	253	0.00 (12.72)	262	2.00 (11.33)		64.9	-2.00 [-4.08, 0.08]
Total (95% CI)	494		511			100.0	-2.44 [-4.12, -0.76]

Test for heterogeneity chi-square=7.08 df=2 p=0.03 I^2 =71.7%

Test for overall effect z=2.85 p=0.004



Clinical efficacy on global function

- **CIBIC-plus**
  - **0.3 - 0.5 point on CIBIC**

CLINICIAN INTERVIEW BASED IMPRESSION OF CHANGE
SUMMARY SHEET

THREE – SIX MONTH VISIT

Overall Score – Clinical Impression of Change:

- ❑ Very Much Improved
- ❑ Much Improved
- ❑ Minimally Improved
- ❑ No change
- ❑ Minimal worsening
- ❑ Moderate worsening
- ❑ Marked worsening

Pharmacokinetics of AChEIs

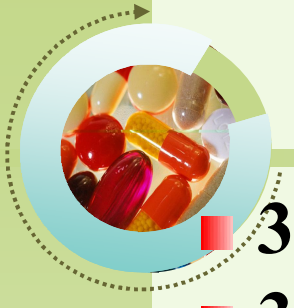
Drug	T_{max} (h)	Half-life (h)	Hepatic metabolism
Donepezil	3-5	60-90	CYP1A2, CYP2D6
Rivastigmine	0.8-1.8	2	Nonhepatic
Galantamine	0.5-2	5-7	CYP2D6, CYP3A4

Safety & Tolerability of AChEIs

- Generally safe & S/E limited to GI symptoms
  - ↓with low dose & slow titration
  - Higher during initiation & increase before steady-state
- Relative contraindications
  - Acute peptic ulcers
  - Severe asthma
  - Bradycardia (<50/min)
  - First degree heart block
  - Obstructive urinary disease
- Drug-associated mortality (?)

Dose & Side effect of AChEIs

Drug	Initial dose	Maintenance dose	Common S/E	Uncommon S/E
Donepezil	5mg for 4-6 wks	10mg/d	nausea, diarrhea, vomiting	insomnia, bad dreams, dizziness
Rivastigmine	1.5mg bid for 2wks, 1.5mg ↑ every 2-4wks	3-6mg bid	nausea, diarrhea, weight loss, vomiting	Dizziness, Fatigue, headache
Galantamine (Reminyl ER)	4mg bid for 4wks 4mg ↑ every 4wks (8mg ER)	8-12mg bid (16-24mg ER)	nausea, vomiting, diarrhea, dizziness	weight loss, headache, abdominal pain, asthenia, somnolence



Comparison between AChEIs

- 3 drugs equally effective and safe
- 3 open & 1 double-blind, randomized

1: Curr Med Res Opin. 2005 Aug;21(8):1317-27.

Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period

Bullock R, Touchon J, Bergman H, Gambina G, He Y, Rapatz G, Nagel J, Lane R.

1: Int J Clin Pract. 2002 Jul-Aug;56(6):441-6.

A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease.

Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, Maud CM, Engelbrecht I, Hock C, Ieni JR, Bahra RS.

Cost effectiveness of AChEIs

- One of standard care in the U.S.
- English Consortium : not effective
  - Limited evidence on quality of life & institutionalization

Donepezil Is Associated with Delayed Nursing Home Placement in Patients with Alzheimer's Disease

David S. Geldmacher, MD,† George Provenzano, PhD,‡ Thomas McRae, MD,§ Vera Mastey, MS,‖ and John R. Ieni, PhD¶*

DONEPEZIL DELAY TO NURSING HOME PLACEMENT STUDY IS FLAWED

NICE proposes to withdraw Alzheimer's drugs from NHS

Zosia Kmietowicz *London*

Several other issues on AChEIs

- How long should be treated?
  - Benefits may last at least 4 years
- Is it useful to switch from one AChEI to another?
- Is it reasonable to discontinue if no noticeable benefit?
  - Benefit may only be apparent after discontinuation
- AChEI vs BChEI
- No need of tapering for discontinuation
- No reason to combine two or more AChEIs

Antiglutamatergic Tx : Memantine

- NMDA antagonist
  - Specific, low- to moderate-affinity, uncompetitive
  - Prevention of neurotoxic calcium influx
- Pharmacokinetic profiles
  - Half-life (h) : 60-80, nonhepatic
  - Not altered by food, gender or age
- Development & approval
  - Developed at Eli Lilly (1963)
  - Marketed in several European countries (1982)
  - Approved in Europe (2002.2)
  - Approved by the FDA (2004.1)

Clinical efficacy

- **Moderate to severe AD**
  - **Cognitive, functional, global benefit**
- **Benefit in milder stage is unclear**
- **5mg/d → 5mg every 2wks → 10mg bid**
- **May be useful for AD, VD and mixed dementia**

Three multicenter, randomized, double-blind clinical trials

	Winblad & Poritis,1999	Reisberg et al, 2003	Tariot et al, 2004
Number	166	252	404
Mean age	71.2	76	75.5
Baseline MMSE	6.3	7.9	10.1
Dose (mg/day)	10	20	20 as add-on to aricept
Length (weeks)	12	28	24
Primary endpoint	CGI-C, BRP	ADCS-ADL, CIBIC-plus	ADCS-ADL, SIB

Clinical efficacy in mild AD

1: Am J Geriatr Psychiatry. 2006 Aug;14(8):704-15.

Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial.

Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, McDonald S.

- **Randomized, double-blind, placebo-controlled trial**
- **403 outpatients (memantine : 201, placebo : 202)**
- **MMSE score : 10-22**
- **ADAS-cog, CIBIC-plus, NPI, ADCS-ADL**
- **Better outcomes on cognition, global status & behavior**

Safety & tolerability

- Data from over 100,000 patient
- Low potential for interaction
- Overall incidence of adverse events was similar to placebo
  - 22% vs 21% (Winblad), 9.5% vs 5.0% (Peskind)
  - 84% vs 86% (Reisberg), 78% vs 72% (Tariot)
- Frequent adverse events
  - Agitation, urinary incontinence, insomnia, UTI, diarrhea

Combination therapy with AChEIs

1: Am J Geriatr Psychiatry. 2006 May;14(5):428-37.

A responder analysis of memantine treatment in patients with Alzheimer disease maintained on donepezil.

van Dyck CH, Schmitt FA, Olin JT; Memantine MEM-MD-03 Study Group

Vitamin E

- Clinical efficacy
  - Delay in institutionalization
  - Preventive effect is controversial
  - Combination of vit.C with vit. E showed protective effect
  - No effect in MCI patients
- Safety issues
  - Falls & syncope
  - High dose(≥400IU) may increase mortality

Ginkgo biloba

- **Mechanism of effect**
  - **Antioxidant properties**
  - **↓ aggregation of the amyloid β protein (Aβ)**
- **Clinical effect**
  - **1.7 points in ADAS-cog (52 wks)**
- **Safety**
  - **Most formulations appear safe**

NSAIDs

- **Protective effect against the development of AD**
  - **Meta-analysis of nine studies : lower risk**
  - **Prospective studies are not enough**
  - **Not effective after AD development**
  - **Not recommended for AD treatment**

γ secretase

- Problematic S/E can be occur
  - APP is not the only or even the preferred substrate
  - Notch receptor is one of the important substrate
  - Profound alterations in thymocyte differentiation
- Clinical trials
  - Only a few preliminary results
  - ↓Aβ in plasma but not in the CSF

β secretase

- Development has proved challenging
- Clinical trials
  - None has been tested extensively in human
  - ↓Aβ in plasma but not in the CSF

Immunotherapy

- Prevention of pathology in AD transgenic mice
  - Active immunization
  - Passive immunization
- Active $A\beta_{42}$ immunization in human
  - Meningoencephalitis in 6% of patients
  - The highest titers showed the least cognitive decline
  - Reduced amyloid burden in two immunized cases
- Passive immunization in human