

European Perspective: the rationale of current and future Pharmacotherapeutics in Alzheimer's disease

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Greenland

Netherlands
Belgium

Iceland

Sweden
Finland

Norway

Denmark

United
Kingdom

Ireland

Germany

Poland

Belarus

Russia

Estonia
Latvia
Lithuania

France

Austria

Czech

Slovakia
Hungary

Ukraine

Italy

Romania

Moldova
Serbia &
Montenegro

Portugal

Spain

Slovenia

Bulgaria

Georgia

Turkey

Switzerland

Malta

Greece

Cypus

Bosnia Herzegovina

Croatia

Albania

Macedonia

SYMPTOMATIC DRUGS

- Cholinesterase inhibitors
(donepezil, rivastigmine,
galantamine)
- NMDA-receptor
antagonist (memantine)

!!!

FUTURE

DISEASE MODIFYING DRUGS

???

The current treatment options: Symptomatic AD drugs

Trials for registration purposes are based on **6-12 months** efficacy and safety data showing superiority over placebo on:

- cognitive (ADAS-Cog, a performance based measure),
- functional (activities of daily living)
- and global domains (CIBIC, the Clinician Interview Based Impression of Change with Caregiver Input)
- Reimbursement on country level

Clinical benefits of symptomatic AD drugs beyond 6 – 12 months ?

- AD2000 Collaborative Group (Lancet 2004): Based on long-term (3 yrs), double-blind, randomized trial including 565 patients with Alzheimer's disease the authors' conclusion was "***Donepezil is not cost effective, with benefits below minimally relevant threshold***"
- ***BUT: n < expected, high drop out rate, diagnostic criteria excluded neuroradiological imaging or other diagnostic tests***
- ***SO: "Donepezil without supportive treatments in heterogenous, unselected population is not cost-effective" (Prof Kaisu Pitkälä, Univ of Helsinki, Finland, Lääkärilehti 2004)***

Recent long-term trials on symptomatic drugs

- **Farlow MR et al. (2005)** Rivastigmine: an open-label, observational study of safety and effectiveness in treating patients with Alzheimer's disease for up to 5 years. *BMC Geriatrics* 5:3.
- **Burns et al. (2007)** Efficacy and safety of donepezil over 3 years: an open label, multicentre study in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 22
- Donepezil vs. placebo in patients with **severe AD**:
 - **Winblad B et al. (2006)** *Lancet*; 367:1057-65
 - **Black SE et al. (2007)** *Neurology*; 69:459-469

Initiation and Continuation of Treatment in Europe (25 countries)

Initiation
Specialists

Continuation
Specialists

15

10

Proportion Under Treatment

Country	Percent under treatment
Austria	32
Belgium	30
Bulgaria	6
Czech Rep.	9
Denmark	28
Finland	30
France	50
Germany	26
Hungary	3
Ireland	46
Italy	18
Netherlands	8
Poland	16
Portugal	33
Slovak Rep.	10
Spain	40
Sweden	47
Switzerland	28
UK	18

CARE MANAGEMENT

- Early diagnosis of dementia
- Treatment of comorbidities
- Avoidance of unnecessary comedications
- Rehabilitation
- Follow-up

Suhonen J et al (2008, Lääkärilehti): Finnish Recommendations for best practices in the treatment of progressive memory disorders.

Finnish estimates of dementia costs (Suhonen J et al 2008)

- In the year 2005:

Annual average cost per patient was 24 000 € most of which (85 %) is related to the long-term institutional care and only 1% involving expenditure related to the diagnosis

Comprehensive care management & cost-efficacy

- **Lupsakko T et al. (Lääkärilehti 2008):** A study conducted in a Finnish general medicine ward between 2001-6 demonstrated how a switch towards a more active and rehabilitative patient care ideology (e.g. new geriatrist physiotherapist, an exercise room & home help services) resulted in:
 - Decline in average time spent on ward from 31 to 13 days.
 - Reduction in relative amount of institutional care among patients aged over 75 years from 10% to 6%.
 - Reduction in average utilisation of the ward from 93% to 85%

Conclusions on symptomatic AD drugs

- Currently licenced AD drugs can be considered clinically meaningful (and as such cost-effective) when used

as a part of a good clinical care management in patients with mild, moderate or even severe AD,

which requires an adequate expertise, experience & memory clinics

Future: Disease modifying drugs

- European task force consensus, Lancet Neurol 2007
 - Defining the concept of disease-modifying treatments
 - Is there a role for biomarkers ?
 - Determining trial designs that should be used?

The concept of disease-modifying treatments

- US Food and Drug Administration (FDA): *“an effect on the pathophysiological process (mechanistic approach) must be shown”*
- European Medicines Agency (EMA): *“the potential approval of a disease modifying drug must be based on sound clinical outcomes”*

→Wording of indication: *“...**slowing**...”* vs. *“**modifying** of disease progression...”*

Is there a role for biomarkers ?

- A surrogate endpoint that could substitute clinical endpoints needs yet to be shown
- The increased tau and reduced amyloid- β in the cerebrospinal fluid may help in early diagnosis of AD and differential diagnostics

Study designs

- Due to the available symptomatic drugs most clinical trials are likely being conducted as an add-on design
 - a minimum of 18 months study duration
 - a reduction in the progression rate of 30-50%
 - given the natural span of 10 years, a delay in disease progression should be minimum of 3 - 6 months but ideally > 6 months (?!)

Potential flaws (I)

- **Diagnostics**

”pure AD” vs. mixed AD + VAD cannot be differentiated in a reliable way

Accumulating evidence suggests that mixed AD+VAD is the most common type of dementia

→

Can patients with vascular risk factors be diagnosed with ”pure” AD ?

Potential flaws / diagnostics cont. (II)

Current practice: Official indications include only AD, not AD+VAD & new interventions are intended for the officially approved indication i.e. AD directing, thus, the clinical diagnostics

....

resulting, thus, in heterogenous target population and, consequently, highly variable rate of disease progression

Potential flaws (III)

- **Long-term effects of symptomatic AD drugs ? > 1 year at least in some individuals ?**

→

Is study duration of 18 months sufficient to show efficacy of new add on therapies?

→

What is the additional benefit, if any, obtained with the disease modifying drugs ?

FUTURE CHALLENGES

- Will new disease modifying drugs replace the current symptomatic drugs ?
- How long the treatment with disease modifying drugs should be continued?
- The role of current and potential new interventions in other but AD dementias?

Conclusions on potential new disease modifying drugs

- The efficacy data needs to be robust to show EBP of a new intervention as add-on therapy due to
 - diagnostics (AD vs. AD+VAD) and, thus,
 - large interindividual variation in the rate of disease progression



Authorization and Reimbursement in Europe

Country	Donepezil		Rivastigmine		Galantamine		Memantine	
	Authorized	Reimbursed	Authorized	Reimbursed	Authorized	Reimbursed	Authorized	Reimbursed
Austria	1	1	1	1	1	1	1	1
Belgium	1	1	1	1	1	1	1	1
Bulgaria	1	0	1	0	1	0	0	0
Cyprus	1	1	1	1	1	1	1	1
Czech Rep.	1	1	1	1	1	1	1	1
Denmark	1	1	1	1	1	1	1	1
Estonia	1	1	1	0	1	1	1	1
Finland	1	1	1	1	1	1	1	1
France	1	1	1	1	1	1	1	1
Germany	1	1	1	1	1	1	1	1
Greece	1	1	1	1	1	1	1	1
Hungary	1	1	1	1	0	0	1	1
Iceland	1	1	1	1	1	1	1	1
Ireland	1	1	1	1	1	1	1	1
Italy	1	1	1	1	1	1	1	0
Latvia	1	0	1	0	1	0	1	0

Authorization and Reimbursement in Europe (cont'd)

Country	Donepezil		Rivastigmine		Galantamine		Memantine	
	Authorized	Reimbursed	Authorized	Reimbursed	Authorized	Reimbursed	Authorized	Reimbursed
Lithuania	1	1	0	0	1	0	1	1
Luxembourg	1	1	1	1	1	1	1	1
Malta	1	0	1	0	1	0	1	0
Netherlands	0	0	1	1	1	1	1	1
Norway	1	1	1	1	1	1	1	0
Poland	1	1	1	1	1	0	1	0
Portugal	1	1	1	1	1	1	1	1
Romania	1	1	1	1	0	0	1	1
Slovak Rep.	1	1	1	1	1	1	1	1
Slovenia	1	1	1	1	1	1	1	1
Spain	1	1	1	1	1	1	1	1
Sweden	1	1	1	1	1	1	1	1
Switzerland	1	1	1	1	1	1	1	1
Turkey	1	1	1	1	1	1	1	1
UK	1	1	1	1	1	1	1	0
	30	27	30	26	29	24	30	24

Initiation and Continuation of Treatment in Europe

Country	Initiation Specialists (1=yes)	Continuation Specialists (1=yes)
Austria	1	1
Belgium	1	1
Czech Rep.	1	1
Denmark	0	0
Finland	0	0
France	1	0
Germany	0	0
Greece	1	0
Hungary	1	1
Iceland	0	0
Ireland	0	0
Italy	1	1
Luxembourg	0	0
The Netherlands	1	1

Initiation and Continuation of Treatment in Europe (cont)

Country	Initiation Specialists (1=yes)	Continuation Specialists (1=yes)
Norway	0	0
Poland	0	0
Portugal	1	1
Romania	1	1
Slovak Rep.	1	1
Slovenia	1	0
Spain	1	1
Sweden	0	0
Switzerland	0	0
Turkey	1	0
UK	1	0
	15	10