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GUIDELINES

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Alzheimer's disease and other dementias

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Abstract

Objectives. To define a practice guideline for biological treatment of dementia and to make transparent the development of the guideline connecting the original data with the resulting recommendations. *Methods.* This guideline includes pharmacologic treatment considerations for patients with Alzheimer's disease, vascular dementia, DLB, and fronto-temporal dementia. Studies were selected that represent double-blind placebo-controlled trials of at least 3 months duration in patients with a diagnosis of dementia according to accepted international diagnostic criteria (for example the NINCDS/ADRDA or NINDS/AIREN criteria). Moreover, to be included studies had to fulfill a restrictive set of methodological criteria. Original studies and not meta-analyses determined the evaluation and the development of recommendations. *Results.* Antidementia pharmaceuticals neither cure nor arrest the disease. A modest effect of improvement of symptoms compared with placebo can be observed. Antidementia pharmaceuticals show different efficacy and side effect profiles. The type of dementia, the individual symptom constellation and the tolerability should determine what medication should be used. There are hints that combination therapy of drugs with different therapeutic mechanisms might improve the efficacy. In treating neuropsychiatric symptoms (NPS), psychosocial intervention should be the treatment of first choice. Pharmaceuticals can only be recommended when psychosocial interventions is not adequate. However, even then the side effects of pharmaceuticals limit their use. *Conclusions.* Depending on the diagnostic entity and the pathology treated different anti-dementia drugs can be recommended to improve symptoms. In the management of NPS, side effects limit the use of medications even when psychosocial interventions have failed. Thus, there is an urgent need to develop more efficacious medications for the treatment of dementia.

Key words: *Dementia, guidelines, Alzheimer, vascular dementia, Lewy body disease, fronto-temporal dementia, anti-dementia pharmaceuticals, neuropsychiatric symptoms, NPS, biological, treatment*

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Table VI. Doses of drugs with methodologically adequate RCTs.

Generic name (alphabetic order)	Functional classification primary pharmacological action	Starting dose (mg/day)	Standard dose (mg/day)
Donepezil	Cholinesterase inhibitor	5 for at least 4 weeks	10
Galantamine	Cholinesterase inhibitor	8 for four weeks	16–24
Ginkgo biloba EGb761	Free radical scavenger, mitochondrial protection	240	240
Memantine	Glutamate-receptor-modulator	5 (weekly increase by 5 mg)	20
Rivastigmine	Cholinesterase inhibitor	3 (2×1.5) minimally for 2 weeks	12
		4.6 mg Patch	9.2

are cholinesterase inhibitors. Memantine is a NMDA-channel modulator and Ginkgo biloba a phytopharmacon.

In Supplementary Tables 1–10 (available online) an extensive description of all meaningful studies can be found including a rating of evidence that let to the following conclusions. An overview of all studies included is provided in Table VII.

With respect to the results demonstrated in Table VII, there are no hints that parameters such as the origin of the data and the number of centers influence the outcome. Most studies were funded by the vendor of a substance. The selection criteria took care of including only studies with reasonable methodology.

Most studies investigated age groups with a mean age between 70 and 80 years. The standard deviation of close to 10 years limits conclusions. Evidence decreases with the distance of the age of a patient from the mean age in trials. In most studies the severity level of the disease lay between Global Deterioration Scale (GDS) 3–5. With respect to all studies investigating dementia no significant difference in efficacy could be detected between AD and VD. Thus from a data point of view, the same recommendations will cover both diseases. This outcome might also be supported by recent pathological considerations (see above). However, authorities differentiate between the two indications and often only license the use in AD.

When all areas of efficacy are observed, every anti-dementia drug showed an individual evidence profile. In at least one parameter investigated according to the methodological criteria outlined above, all substances demonstrated statistical efficacy. This means all drugs demonstrate a modest benefit (i.e. no cure, no arrest, just symptom improvement for a limited time in a part of the patients). For each individual symptom profile, the efficacy data would allow to select the best available substance. However, the pharmaceuticals differ in side effects (Table VIII). For treatment, side effects and efficacy will have to be taken into account.

Side effects

Frequent (i.e. higher than 1/100 patients) and very frequent (i.e. higher than 1/10 patients) side effects of these substances are shown in Table VIII. The studies give no hint of other side effects or of a higher probability for a particular side effect.

Comparison of results with recent reviews and meta-analyses

Cholinesterase inhibitors

Physostigmine demonstrated efficacy in treating dementia (see review in Möller et al. 1999). Further substances were developed that could be taken orally. The three cholinesterase inhibitors used in the treatment of dementia: donepezil, galantamine, and rivastigmine, are generally started at a low dose and increased when no side effects appear. Reviews underline the described efficacy of cholinesterase inhibitors (Clegg et al. 2001; Birks et al. 2009; IQWiG 2007; Prvulovic et al. 2010). For cholinesterase inhibitors, basic scientific studies show that there is an individual dose-response relationship. Every individual has a dose that is too low to cause any effect. In a higher dose cognitive function will improve. However, if this dose is increased further no improvement but side effects can be seen (Ihl et al. 1989). For each patient, from a biological point of view to titrate the necessary dose would be useful. In clinical studies the dose is increased slowly but not titrated. Moreover, the studies did not systematically exclude all substances with anticholinergic side effects. Thus, a part of the results might be ascribed to extinguishing side effects.

Memantine. For memantine in "moderate to severe" dementia, recent reviews and meta-analyses support the findings (Gauthier et al. 2008; Ferris et al. 2009).

Ginkgo biloba extract. For Ginkgo biloba extract, independent meta-analyses in addition to the data

Table VIII. Side effects of anti-dementia pharmaceuticals: Side effects with a probability of 1/10 and higher are marked bolt.

Generic Name (in alphabeticorder)	Contraindication	Nausea/gastro-intestinal	Sleep	Behaviour	Neurological	Others
Donepezil	Hypersensitivity on piperidin derivates	**Diarrhoea, nausea,** vomiting, loss of appetite, gastro-intestinal complaints	Tiredness, sleeplessness	Hallucinations, agitation, aggressive behavior,	**Headache** muscle cramps, syncope, dizziness, ache	Cold, accidents, rash, itch, incontinence of the bladder, dyspnea
Galantamine	Severe liverand renal dysfunction	**Nausea, vomiting,** reduced appetite, weight gain, abdominal pain, dyspepsia, gastro-intestinal complaints	Sleeplessness somnolence	Asthenia, confusion, depression, fatigue, indisposition	dizziness syncope, tremor, headache	Rhinitis, uro-genital infections fever, falls, injury, dyspnea
Ginkgo biloba	None	None	None	None	None	None
EGb761						
Memantine	Severe liver & renal dysfunction	Constipation	Tiredness	Irritability	Dizziness, headache	Increased blood pressure
Rivastigmine	Severe liver dysfunction, hypersensitivity on Carbamate derivates	**Nausea, vomiting,** diarrhoea, loss of appetite, abdominal pain, dyspepsia, loss of weight	Somnolence, tiredness	Agitation, confusion, asthenia	dizziness, headache, tremor, syncope	Increased sweating, dyspnea

support the findings (IQWiG 2008; Kasper and Schubert 2009; Wang et al. 2010).

Comparison studies

Although there are many methodological issues, there is a consistency in the data which is similar to other fields of treatment with psychopharmaceuticals. There are no studies demonstrating superiority of cholinesterase inhibitors over memantine or ginkgo biloba or vice versa.

Cost effectiveness

From a costs perspective, treatment with anti-dementia pharmaceuticals will reduce costs (Wimo et al. 2003).

Other anti-dementia pharmaceuticals

A wide group of other agents with diverse mechanisms of action have been tested in at least one randomized controlled clinical trial, but there is incomplete or conflicting evidence for these agents. In particular, intravenous cerebrolysin, a neurotrophic brain extract, improved global functioning and activities of daily living in one trial. For treatment in AD, several negative studies have been reported including an ACTH analog, DGAVP; the nootropics aniracetam, BMY21, 50139 and piracetam; and two trials of phosphatidyl serine. Other negative randomized controlled clinical studies include the NMDA receptor stimulator cycloserine, besipiridine, and milacemide. Hydergine was ineffective at 3 mg per day and showed slight memory improvement at 6 mg day, but did not meet a priori benefit standards. Patients receiving acetyl-L-carnitine, a membrane-stabilizing agent, showed less decline over one year on 4 of 14 neuropsychologic measures, but the drug was ineffective in a second study. Idebenone, a coenzyme Q analog, showed mild improvement in some neuropsychologic tests and produced a significant drug–placebo difference on a global neuropsychologic instrument, but in separate studies. Selegiline produced a modest drug–placebo difference in cognition in a 3-month trial of 136 patients with mild to moderate AD, but not in a 6-month trial with 60 patients. A low dose of nimodipine (30 mg TID) improved memory (but not other measures) but not at a higher dose (90 mg TID). In one large, 2-year trial, selegiline (5 mg BID) and vitamin E (1000 IU [α-tocopherol] BID) significantly delayed the time to a composite outcome of primary measures indicative of clinical worsening, and fewer patients treated with vitamin E were institutionalized. Importantly,