World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Dementias in Primary Care

Ralf Ihl, Robertas Bunevicius, Lutz Frolich, Bengt Winblad, Lon S Schneider, Bruno Dubois, Alistair Burns, Florence Thibaut, Siegfried Kasper, Hans-Jürgen Möller, on behalf of the Wfsbp Task Force on Mental Disorders in Primary Care and Wfsbp Task Force on Dementiay

Doi: 10.3109/13651501.2014.961931

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Results: Anti-dementia medications neither cure, nor arrest, or alter the course of the disease. The type of dementia, the individual symptom constellation and the tolerability and evidence for efficacy should determine what medications should be used. In treating neuropsychiatric symptoms, psychosocial intervention should be the treatment of first choice. For neuropsychiatric symptoms, medications should only be considered when psychosocial interventions are not adequate and after cautious risk-benefit analysis.

Conclusions: Depending on the diagnostic entity and clinical presentation different anti-dementia drugs can be recommended. These guidelines provide a practical approach for general practitioners managing dementias.
World Federation of Societies of Biological Psychiatry (WFSBP)
Guidelines for the Pharmacological Treatment of Dementias in Primary Care

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Short title: Dementia guidelines for primary care

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Keywords: Dementia, guidelines, Alzheimer’s disease, Lewy body disease, anti-dementia drugs, neuropsychiatric symptoms
Introduction
Dementia is a syndrome of acquired cognitive deficits sufficient to interfere with social or occupational functioning, which results from various central brain pathological processes. Deficits in cognitive domains include global cognitive function, orientation, memory impairment, concentration and calculation, language, visuoperceptual skills and executive, instrumental and basic functions. The syndrome is diagnosed in association with behavioral assessment, neuroimaging and laboratory investigations.
Dementia has become a major public health problem due to its increasing prevalence accompanying the aging of the population, long duration, caregiver burden, and high financial cost of care. The prevalence of dementia increases continuously with age and has been estimated to be about 1% in the group aged 65 – 69 years and 29% at age 90 years and older. The most frequent underlying neurobiological cause of a dementia syndrome is Alzheimer’s disease (AD), accounting for at least 60% of dementia in patients older than 65. Table 1 gives an overview of different types of dementia.
A long pre-clinical period precedes development of Alzheimer disease dementia. The border zone between normality and dementia most frequently is called as mild cognitive impairment, originally described in association with stage 3 on the Global Deterioration Scale. For this zone, so far the definition process is not finalized. However, careful clinical evaluation allows the assessment for ‘mild cognitive impairment due to Alzheimer disease’ and ‘prodromal Alzheimer disease,’ which is Alzheimer disease before the onset of the dementia (Albert et al 2011, Dubois et al 2010). From a clinical perspective, dementia predominately affects cognition, behavior/mood, physical functions, and activities of daily living and leads to caregiver burden. The clinical course varies depending upon the origins of the dementia syndrome and often is characterized with combinations of different dementia pathologies.

General management principles for dementia
After the diagnostic procedure the physician in charge of the treatment and care of the patient should schedule regular follow-up visits. The purposes of planning systematic follow-ups include:
• To ensure identification and appropriate treatment of concomitant conditions and complications of the primary dementia disorder.
• To evaluate cognitive, emotional and behavioral symptoms.
• To assess caregiver burden and needs.
• To assess sources of care and support.
• To provide continuous advice and guidance to patients and caregivers on health and psychological issues.
• To administer appropriate caregiver interventions.
It is important to follow legal requirements for informed consent in prescribing medications. For persons with dementia unable to give informed consent, proxy consent should be obtained from their family caregiver or other appropriate person as required by local legislation.

Anti-dementia treatments
From a pharmacological perspective, all interventions for dementia target at least one of the following broad therapeutic goals
(1) Prevention of onset of dementia (this applies to those at greatest risk; notably, preventing those with MCI from progressing to a dementia syndrome);
(2) Symptomatic treatment of dementia (stabilization or improvement of the current cognitive, behavioral, functional, or caregiver status);
(3) Delay in the progression of dementia symptoms (stabilization or improvement of cognitive, behavioral, and functional symptoms in the patient or caregiver status OR minimize decline of the disease symptomatic progression)
The WFSBP Task Force for Dementia conducted a computer-based literature research in order to examine the issue. On the basis of this evidence, guidelines are suggested. The WFSBP criteria to determine the evidence and recommendations can be found in
table 2 (level of evidence) and 3 (grade of recommendation). With respect to data most of the recommendations in this guideline did not achieve a higher grade than 3. To come to more valid conclusions, further research will be necessary. The following recommendations can be given:

1. For prevention, medications so far cannot be recommended (Evidence level D, recommendation grade 5)
2. For curing or arresting of AD or VD or other types of degenerative dementias, no drugs can be recommended.
3. Only for the symptomatic treatment of Alzheimer disease dementia is there sufficient data available (Evidence level B, recommendation grade 3). The cholinesterase inhibitors donepezil, galantamine and rivastigmine show a modest positive effect over a limited time, in a subgroup of treated patients. For the NMDA-modulating medication memantine and the radical scavenger and mitochondria protecting ginkgo biloba extract, this was also demonstrated. For symptomatic treatment of AD, these medications can be recommended (doses presented in Table 4). Donepezil, galantamine, and rivastigmine are associated with significant side effects and memantine and ginkgo biloba extract have fewer side effects (Table 5). Methodological inadequacies prohibit a systematic recommendation of medications related to specific severity levels or other aspects of Alzheimer disease except that memantine appears to be most effective in moderate to severe dementia.
4. Cholinesterase inhibitors have been shown to be useful for cognitive and neuropsychiatric symptoms in dementia with Lewy bodies (Donepezil and Rivastigmine) and Parkinson's disease dementia (Rivastigmine).
5. A significant percentage of patients with Lewy body dementias experience severe neuroleptic sensitivity reactions and these drugs should therefore be avoided whenever possible (Evidence level B, recommendation grade 3).
6. In frontal lobe dementia the potential risk of increased agitation and behavioral problems with cholinesterase inhibitors has to be considered.
7. Optimal management of vascular risk factors (for instance hypertension, diabetes, optimal cholesterol and lipid levels) and sufficient treatment of accompanying somatic diseases are recommended (Evidence level A, recommendation grade 1).
8. Lithium does not have a positive effect in AD. Anti-epileptic treatment with valproate is ineffective.

Neuropsychiatric Symptoms (NPS) in dementia

Often dementia is accompanied by neuropsychiatric symptoms (NPS; also named as behavioral and psychological symptoms in dementia, BPSD). Examples are
- hyperactivity (agitation, aggression, disinhibition, irritability, aberrant motor behavior);
- affective symptoms (depression, anxiety);
- psychosis (delusions, hallucinations).

A detailed description can be found in Gauthier et al. (2010).

Causative factors of NPS differ in part depending upon the cause of dementias. Somatic diseases and conditions as well as side effects of drugs given for somatic diseases contribute to NPS. Anticholinergic side effects of a broad spectrum of drugs or side effects of glucocorticoids are examples. Unmet needs like hunger, thirst or missing attention may cause NPS; for example screaming might lead to social attention. Environmental factors also may influence the occurrence of NPS (e.g., darkness, excessive heating or cooling, abnormal odors, excessive noise, overcrowding, poor design or institutional settings).

Dementia may also lead to somatic complications like seizures, spasticity, incontinence and swallowing difficulties. Some of these problems occur inevitably in a stage-dependent manner with the progression of dementia, for example, urinary and fecal incontinence with the progression of Alzheimer’s disease. When these symptoms are
treated drug interactions may confound overall treatment aims (example: anticholinergic treatment of incontinence).

**Recommendations for the treatment of NPS**

**Elimination of causal factors:** At first, modifiable causal factors have to be identified and addressed. Thus, somatic disease or side effects of medications need to be identified as possible causal and/or contributing factors. Environmental factors and basic needs such as hunger and thirst may be readily addressed.

**Psychosocial interventions:** To identify subsequent interventions, after the diagnosis of dementia all available caregivers should be seen by the family practitioner. All necessary information should be obtained and caregivers should receive information and training regarding the patient’s condition and the causes of the patient’s behaviors. Moreover, possible additional support should be considered and training in psychosocial aspects of caring should be recommended.

**Treatment with drugs:** When psychosocial interventions and the exclusion of environmental factors fail drug treatment may be necessary. For drug treatment in NPS, recommendations reach only expert opinion standard and are not given here (Evidence level C3, recommendation grade 4). A detailed review of the cautions that have to be taken into account for treating NPS with drugs is given in Gauthier et al. (2010).

Exceptions may occur when the behavior requires urgent attention such as in cases of dangerous aggression; in these cases pharmaceutical treatment may need to be started in tandem with other measures.

**Conclusions**

Dementia is an interdisciplinary challenge, where psychiatrists, neurologists and family doctors have equal importance in the management of the disorder.

For Alzheimer disease dementia treatment with anti-dementia drugs combined with non-pharmacological treatments and if necessary treatment with drugs for behavioral symptoms may provide benefits and improve quality of life in dementia patients and their caregivers. However, at the present time dementia cannot be cured or arrested and the fundamental dementia pathologic process cannot be slowed.

When neuropsychiatric symptoms appear, causative factors like side effects of drugs, thirst, hunger or pain have to be ruled out. If symptoms persist, psychosocial intervention will be the treatment of first choice. For efficacy of pharmaceutical treatment in NPS, the evidence is limited. Moreover, possible side effects need to be carefully considered in the selection and usage of medications for these symptoms.

**Key Points**

- This short version of an evidence-based guideline may improve management of dementia at the primary care level.
- The recommendations are based on randomized controlled studies, which do not always reflect clinical reality, and clinical reality does not always reflect clinical reality.

**Acknowledgements**

None

**Disclosure of Interests**

The development of these guidelines was not supported by any pharmaceutical company.

Ralf Ihl received grants/research support or was involved as consultant, speaker or in advisory boards or received author honoraria within the last three years from APK, Austroplant, BDI, Beltz Test, BOD, Caritas Siegen, Double Helix Development, Eisai, Friedrichverlag, GE Healthcare, Hogrefe, IFE, Janssen, KDA, Landesinitiative Demenz Service NRW, LVR Dueren, Lundbeck, Medical Tribune, Med. Komm., Novartis, Pfizer, Pfrimmer Nutritia, Pierrel, Schwabe, Thieme, Urban & Vogel, Westermayer.

Robertas Bunevicius has received grants/research support, consulting fees and honoraria within the last 3 years from Lundbeck, AstraZeneca, Teva, GlaxoSmithKline

Alistar Burns has no conflict of interest to declare.

Bruno Dubois has received grants/research support, consulting fees and honoraria within the last 3 years from Eli Lilly, Pfizer, Roche
Siegfried Kasper received grants/research support, consulting fees and honoraria within the last three years from AstraZeneca, Bristol-Myers Squibb, CSC, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutica, Lundbeck, MSD, Novartis, Organon, Pierre Fabre, Pfizer, Schwabe, Sepracor, Servier, Wyeth.

Hans-Jürgen Möller has received grant/research support, consulting fees and honoraria within the last years from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, MSD, Novartis, Organon, Otsuka, Pfizer, Schwabe, Sepracor, Servier, and Wyeth.

Lon Schneider has received grants from the NIH P50 AG05142, R01 AG033288, and R01 AG037561, the State of California, the Alzheimer’s Association for a registry for dementia and cognitive impairment trials and grant or research support from Baxter, Genentech, Johnson & Johnson, Eli Lilly, Novartis, and Pfizer. He discloses that within the last 3 years, he has served as a consultant for and received consulting fees from Abbvie Laboratories, AC Immune, Allon, AstraZeneca, Baxter, Biogen Idec, Biotie, Bristol-Myers Squibb, Elan, Eli Lilly, EnVivo, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Novartis, Piramal, Pfizer, Roche, Sanofi, Servier, Takeda, Tau Rx, Toyama, and Zinfandel; and in the past from Ipsen and Schwabe.

Florence Thibaut has no conflict of interest to declare.

Bengt Winblad has received research support from Dainippon Sumitomo Pharma Co Ltd and has served as a consultant at Advisory Board meetings for AC Immune, Axon, Diagenic, Eli-Lilly, Johnson&Johnson, Lundbeck, Merz, Novartis, Pfizer, Roche and Servier.

References

### Table Legends

**Table 1. Comparison of diagnostic criteria of different types of dementia.**

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer's Disease (AD)</th>
<th>Vascular Dementia (VD)</th>
<th>Lewy Body Dementia</th>
<th>Frontotemporal Degeneration</th>
<th>Creutzfeldt-Jakob Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special aspects of symptomatology besides the dementia syndrome</td>
<td>Only 50 % show memory deficit early in the course, preserved facade</td>
<td>Early gait disturbance, bladder dysfunction without urologic reason, falls, focal neurological signs</td>
<td>Fluctuation of attention and alertness, recurrent visual hallucinations, extrapyramidal motor features, oversensitivity to neuroleptics, REM sleep disturbance</td>
<td>Emotional flattening, disinhibition, coarsening of social behaviour, visuospatial functions may be relatively preserved in the beginning</td>
<td>Visual and cerebellar disturbances, pyramidal and extrapyramidal symptoms, myoclonus, akinetic mutism</td>
</tr>
<tr>
<td>Course</td>
<td>Slow progression</td>
<td>Step-wise progression with possible partial compensation after a step</td>
<td>As AD</td>
<td>As AD but faster</td>
<td>Rapid progression, most often less than 1 year duration</td>
</tr>
<tr>
<td>EEG</td>
<td>Slowing of electric wave activity related to severity, decreased fast alpha activity associated with faster progression, no alterations also possible</td>
<td>Often focal alterations</td>
<td>Slowing often early in the course</td>
<td>No characteristic alterations</td>
<td>Periodic sharp waves (triphasic waves often present), not with the new variant</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Increased tau and phosphotau, and decreased Aβ in the CSF</td>
<td>None</td>
<td>Reduced uptake of dopamine transporter in corpus striatum (SPECT or PET); reduced uptake on MIBG scintigraphy</td>
<td>None</td>
<td>Increased protein 14-3-3 in the CSF</td>
</tr>
<tr>
<td>Structural Imaging CT/MRI</td>
<td>Atrophy (medial temporal in the beginning, later temporo-parietal, frontal and finally generalized; hippocampal atrophy related to severity)</td>
<td>Multiple infarcts, single strategic infarcts, extensive white matter lesions</td>
<td>Relatively less severe medial temporal atrophy as compared to AD</td>
<td>Lobar frontal and/or temporal atrophy, often asymmetric</td>
<td>Unspecific</td>
</tr>
<tr>
<td>Functional Imaging, glucose hypometabolism on PET</td>
<td>In the beginning temporo-parietal and posterior cingulate, later frontal, finally generalized</td>
<td>In ischemic areas</td>
<td>Predominantly in visual association cortex</td>
<td>Frontal and temporal cortex often asymmetric</td>
<td>Variable</td>
</tr>
<tr>
<td>Neuropathology</td>
<td>Plaques, fibrillary tangles, conglomophil angiopathy</td>
<td>Ischemic lesions</td>
<td>Lewy bodies, alpha-synuclein positive neurites</td>
<td>Astrocytosis, atrophy of lamina I-III in the frontal cortex, microvasculatisation neurophil, alterations in tau and TDP43</td>
<td>Spongiform encephalopathy (increased amyloidosis and microvesicles)</td>
</tr>
</tbody>
</table>
Table 2. Evidence levels of the WFSBP.

A Full Evidence From Controlled Studies is based on: two or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo” in a study with adequate blinding) and one or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists). In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies shows superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfill established methodological standards. The decision is based on the primary efficacy measure.

B Limited Positive Evidence From Controlled Studies is based on: one or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo”) or a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial and no negative studies exist.

C Evidence from Uncontrolled Studies or Case Reports/Expert Opinion

C1 Uncontrolled Studies is based on: one or more positive naturalistic open studies (with a minimum of five evaluable patients) or a comparison with a reference drug with a sample size insufficient for a non-inferiority trial and no negative controlled studies exist.

C2 Case Reports is based on: one or more positive case reports and no negative controlled studies exist.

C3 Based on the opinion of experts in the field or clinical experience.

D Inconsistent Results. Positive RCTs are outweighed by an approximately equal number of negative studies.

E Negative Evidence. The majority of RCTs studies shows no superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo”) or inferiority to comparator treatment.

F Lack of Evidence. Adequate studies proving efficacy or non-efficacy are lacking.

Table 3. The level of evidence determines the grade of recommendation. Depending on the frequency and severity of side effects it may be altered by one step in category A. A precondition is to recognize that the highest possible treatment outcome herein referred to will be a modest decrease of symptoms over a limited period in the course of the disease.

<table>
<thead>
<tr>
<th>Recommendation grade</th>
<th>Based on</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Category A evidence and good risk-benefit ratio</td>
</tr>
<tr>
<td>2</td>
<td>Category A evidence and moderate risk-benefit ratio</td>
</tr>
<tr>
<td>3</td>
<td>Category B evidence</td>
</tr>
<tr>
<td>4</td>
<td>Category C evidence</td>
</tr>
<tr>
<td>5</td>
<td>Category D evidence</td>
</tr>
</tbody>
</table>
Table 4. Doses of drugs for treatment of Alzheimer disease dementia.

<table>
<thead>
<tr>
<th>Generic name (alphabetic order)</th>
<th>Functional classification (primary pharmacological action)</th>
<th>Starting dose (mg/day)</th>
<th>Standard dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Cholinesterase inhibitor</td>
<td>5 (for at least 4 weeks)</td>
<td>10</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Cholinesterase inhibitor</td>
<td>8 (for four weeks)</td>
<td>16 –24</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Cholinesterase inhibitor</td>
<td>3 (2x1.5) minimally for 2 weeks 4.6 mg Patch the maximum patch dose is 13.3 mg/24 hr</td>
<td>12 9.5</td>
</tr>
<tr>
<td>Ginkgo biloba EGb761</td>
<td>Free radical scavenger, mitochondrial protection</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>Memantine</td>
<td>Glutamate-receptor-antagonist</td>
<td>5 (weekly increase by 5 mg)</td>
<td>20</td>
</tr>
</tbody>
</table>
Table 5. Side effects of anti-dementia medications in patients with Alzheimer disease: Side effects with a probability of 1 in 10 and higher are marked in **bold face**

<table>
<thead>
<tr>
<th>Generic name (alphabetic order)</th>
<th>Contraindication</th>
<th>Nausea/gastro-intestinal</th>
<th>Sleep</th>
<th>Behavior</th>
<th>Neurological</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Hypersensitivity on piperidine derivates</td>
<td><strong>Diarrhea, nausea, vomiting, loss of appetite, gastro-intestinal complaints</strong></td>
<td>Tiredness, sleeplessness</td>
<td>-</td>
<td><strong>Headache</strong>, muscle cramps, syncope, dizziness, ache</td>
<td>Frequent urination, dyspepsia</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Severe liver and renal dysfunction</td>
<td><strong>Nausea, vomiting</strong>, reduced appetite, weight gain, abdominal pain, dyspepsia, gastro-intestinal complaints</td>
<td>Sleeplessness, somnolence</td>
<td>-</td>
<td><strong>Dizziness</strong>, syncope, tremor, headache</td>
<td>Rhinitis, dyspepsia</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Caution if cardiac conduction defects or arrhythmias exist</td>
<td><strong>Nausea, vomiting</strong>, diarrhea, loss of appetite, abdominal pain, dyspepsia, loss of weight</td>
<td>Somnolence, tiredness</td>
<td>Anxiety, confusion, asthenia</td>
<td><strong>Dizziness</strong>, headache, tremor, seizures</td>
<td>Increased sweating, dyspepsia</td>
</tr>
<tr>
<td>Ginkgo biloba EGb761</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Memantine</td>
<td>Severe liver dysfunction</td>
<td>Constipation</td>
<td>Tiredness</td>
<td>Irritability</td>
<td>Dizziness, headache</td>
<td>Increased blood pressure</td>
</tr>
</tbody>
</table>