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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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Preface and disclosure statement

Like with the preceding guidelines of this series (Bauer et al. 2002, Bandelow et al. 2008b), these practice guidelines for the pharmacological treatment of Alzheimer's disease and other dementias (AD) were developed by an international Task force of the World Federation of Societies of Biological Psychiatry (WFSBP). Their purpose is to provide expert guidance on the pharmacological treatment of dementia based on a systematic overview of all available scientific evidence pertaining to the pharmacologic treatment of AD and other disorders associated with dementia. These guidelines are intended for use by all physicians seeing and treating patients with dementia. Some medications recommended in the present guideline may not be available in all countries.

The preparation of these guidelines has not been financially supported by any commercial organization. This practice guideline has been developed mainly by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavours. It is possible that through such activities some contributors have received income related to medicines discussed in this guideline (See disclosure). A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest.

Levels of evidence

The scientific rigor of the data was categorised according to the evidence categories of the World Federation of Societies of Biological Psychiatry (WFSBP, Bandelow et al. 2008a, Table I). Whenever a level of evidence is referred to herein it will be consistent with Table I.

Grade of recommendation

In the current literature, several different "scales" to grade recommendations are used. None of the scales offers any validation data. The grading scale used here was developed and used by the WFSBP (Bandelow et al. 2008b, Table II). To develop recommendations, scientific evidence was taken into account as well as side effects and the highest possible outcome of therapy. For the following recommendations, it is important to remember that available anti-dementia medications neither cure nor arrest the disease. Even the effect on symptoms is modest. For NPS accompanying the disease, treatments following these recommendations might mitigate or even eliminate a particular NPS without influencing the underlying disease.

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. It is defined by the existence of deficits in episodic memory and in other cognitive domains. The syndrome is diagnosed in association with behavioural assessment, neuroimaging and laboratory investigations. Deficits in cognitive domains include global cognitive

Table I. 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") ora randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial andno 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 andno negative controlled studies exist
C3	Based on the **opinion of experts** in the field orclinical experience
D	**Inconsistent Results.** Positive RCTs are outweighed by an approximatelyequal 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 II. 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.

Recommendation grade	Based on
1	Category A evidence and good risk-benefit ratio
2	Category A evidence and moderate risk-benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

function, orientation, memory impairment (e.g., episodic memory), language, visuoperceptual skills and executive functions. Dementia may be diagnosed according to the criteria of the International Classification of Diseases, 10th Revision (ICD-10) (World Health Organisation 1992), or the Diagnostic and Statistical Manual, 3rd ed. (DSM-III) or 4th ed. (DSM-IV) (American Psychiatric Association 1994). The prevalence of dementia may vary with the different diagnostic criteria. Erkinjuntti et al. (1997) compared six commonly used classification schemes (DSM-III, DSM-III-R, DSM-IV, ICD-9, ICD-10, and the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX)). They showed that the prevalence of dementia can differ by a factor of 10 depending on the diagnostic criteria used. Moreover, there are no data on inter-rater-reliability. Two other studies demonstrated that the prevalence of vascular dementia (VD) varies with the classification system and therefore the criteria for diagnosis are not interchangeable. Table III gives an overview of different types of dementia.

International consensus criteria have been developed for several causes of dementia. Alzheimer's disease (AD), the commonest cause of dementia, is diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association criteria (NINCDS/ADRDA, McKhann et al. 1984). Lewy body dementia, which was recognized about a decade ago as possibly the second most frequent cause of neurodegenerative dementia in the elderly, is commonly diagnosed according to the third revision of McKeith criteria (McKeith et al. 2005). The former entities of Pick's disease, frontal lobe dementia, semantic dementia etc. have been combined into the group of fronto-temporal degeneration (FD). Consensus criteria have first been defined by (Neary et al. 1998). Criteria for vascular dementia (VD) have been established by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) workshop (Román et al. 1993). These criteria comprise three entities of cerebrovascular disease: small-vessel disease with extensive leukoencephalopathy (Binswanger's disease), small vessel disease with multiple lacunae (affecting predominantly the basal ganglia and frontal white matter), or large infarcts in strategic locations of large-vessel territories locations.

These subtypes can be distinguished using structural neuroimaging, but almost never occur in pure form (Guermazi et al. 2007). Therefore, it is not surprising that the sensitivity of the NINDS-AIREN criteria is low (about 40% at 95% specificity) at autopsy (Holmes et al. 1999). More than one third of patients with the clinical diagnosis of dementia had the diagnosis of mixed dementia (AD plus cerebrovascular disease) at autopsy (Holmes et al. 1999; Galasko et al. 1994). Vice versa cerebrovascular dysfunction might aggravate the deleterious effects of AD (Iadecola, 2010). These observations might contribute to the explanation of results from clinical studies in vascular dementia using medications for AD (Morris et al. 1988; Tierney et al. 1988; McKhann et al. 1984; Galasko et al. 1994; Nolan et al. 1998; Lim et al. 1999; Román et al. 2010).

The discovery that a long pre-clinical period precedes AD has led to the development of early diagnostic indices of dementia. This border zone between normality and dementia has been given numerous names and definitions, which include: benign senescent forgetfulness (BSF), age associated memory impairment (AAMI), age-consistent memory impairment (ACMI), age-associated cognitive decline (AACD), mild cognitive impairment (MCI), cognitive loss no dementia (CLOND), and cognitive impairment but not dementia (CIND). The prevalence for this pre-clinical or mild form of cognitive decline varies with the classification system used (Schroder et al. 1998). Originally described by Reisberg as a stage in the Global Deterioration Scale (GDS Stage 3, Reisberg et al. 1987) and proven in a study by Flicker et al. (1991) MCI is emerging as the preferred term for this condition. Criteria were published by Peterson et al. (1997) and consensus criteria by Winblad et al. (2004). Ritchie et al. (2001) estimated the prevalence of MCI in the general population to be 3.2% with an 11.1% conversion rate to dementia within a 3-year period. Other studies have found higher rates of conversion (Geslani et al. 2005; Amieva et al. 2004), probably related to the exact definition of MCI and population sampled. Recently, the criteria of MCI have been refined into single domain and multiple domain MCI (one or several

Table III. Comparison of diagnostic criteria (for biomarkers see Wiltfang et al. 2005; for CT/MR Frisoni et al. 2010; for PET Nordberg et al. 2010; for EEG Rossini et al. 2007).

	AD	VD	LBD	FD	CJD
Special aspects of symptomatology besides the dementia syndrome	Only 50 % show memory deficit early in the course, preserved facade	Early gait disturbance, bladder dysfunction without urologic reason, falls, focal neurological signs	Fluctuation of vigilance, paranoid and hallucinatory symptoms, Parkinsonian rigidity, oversensitivity to neuroleptics, REM sleep disturbance	Euphoria, emotional flattening, disinhibition, coarsening of social behaviour, visuo-spatial functions preserved in the beginning	Visual and cerebellar disturbances, pyramidal and extrapyramidal symptoms, myoclonus, akinetic mutism
Course	Slow progression	Step-wise progression with possible partial compensation after a step	As AD	As AD but in comparison faster	Rapid progression, most often less than 1 year duration
EEG	Slowing of electric wave activity related to severity, decreased fast alpha activity associated with faster progression, no alterations also possible	Often focal alterations	Slowing related to severity (as in AD)	No characteristic alterations	Periodic sharp waves (triphasic waves often present), not with the new variant
Biomarker	Increased tau and phospho-tau, and decreased Aβ in the CSF	None	None	None	Increased protein 14-3-3 in the CSF
Structural Imaging CT/MRI	Atrophy (medial temporal in the beginning, later temporo-parietal, frontal and finally generalized; hippocampal atrophy related to severity	Multiple infarcts, single strategic infarcts, extensive white matter lesions	Relatively less severe medial temporal atrophy as compared to AD	Lobar frontal and/or temporal atrophy, often asymmetric	Unspecific
Functional Imaging Glucose hypomeatbolism on PET	In the beginning temporo-parietal and posterior cingulate, later frontal, finally generalized	In ischemic areas	Predominantly in visual association cortex	Frontal and temporal cortex often asymmetric	Variable
Neuropathology	Plaques, fibrillary tangles, congophil angiopathy	Ischemic lesions	Lewy bodies	Astrocytosis, atrophy of lamina I-III in the frontal cortex, microvascualisation neuropil, alterations in tau and TDP43	Spongiform encephalopathy (increased amyloidosis and microvesicles)

cognitive domains are impaired), and amnestic and non-amnestic MCI (primary memory impairment vs. primary impairment of non-memory cognitive functions, Petersen et al. 2001; Petersen, 2004). With the exception of multiple-domain non-amnestic MCI, all other MCI subtypes showed the highest association with AD in a population based study (Busse et al. 2006). The clinical entity of MCI is still not satisfactorily defined. This entity, however, plays a major role in the evaluation of secondary preventive treatments that may have the potential to attenuate or stop the conversion from MCI into dementia. It may be necessary in the future to include neuroimaging and CSF/blood biomarkers to define persons with MCI as at risk for dementia, particularly for AD. However, for clinical studies, the definitions of the concept are often not operationalised robust enough to identify reproducible groups. These aspects may account for the observed variability between samples with MCI (Arnáiz et al. 2004).

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 in Europe 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 (Lobo et al. 2000). 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. Presently, it is estimated that 7.21 million patients in Europe and 3.1 million in North America suffer from mild to severe AD. This number is projected to increase to 16.51 million in Europe and 8.85 million in North America until in the year 2050 (Brookmeyer 2007). In Asia, South America and Africa, the numbers although lower than in Europe and North America now, will quintuple by 2050.

From a clinical perspective, dementia predominately affects cognition, behavior/mood, physical functions, activities of daily living and caregiver burden. Most therapeutic interventions for dementia aim to affect these domains. From a pharmacological perspective, all interventions for dementia try to target at least one of the following broad therapeutic goals.

Prevention of onset of dementia

In the context of this review, this applies to those at greatest risk (such as those with a clinical diagnosis of MCI) of progression to a dementia syndrome.

Symptomatic treatment of dementia

Symptomatic benefit can be described as maintenance (or stabilization) or improvement of the current cognitive, behavioural, functional, or caregiver status only while on active treatment with the pharmacological intervention. Withdrawal of the pharmacological therapy may result in a decline towards baseline or placebo levels of relevant outcomes.

Delay in the progression of dementia

A therapeutic intervention that brings about delay in the progression of the disease can be described as either (1) one that maintains (or stabilizes) or improves current cognitive, behavioural, functional, or caregiver status, which is sustained even when the drug is withdrawn, or (2) one that can be shown to alter the rate of decline of the disease progression, even when the drug is withdrawn.

However, only for the symptomatic treatment of dementia are sufficient data available. In the first section of this guideline, the criteria for the evaluation of studies are described. In the second part, the evidence for the pharmacological treatment options is reviewed and the levels of evidence for the available treatment options evaluated. Finally, on the basis of this evidence, guidelines will be suggested.

Methods

The data used for this guideline have been extracted from a Medline and Embase search, from recent proceedings of key conferences, from meta-analyses and reviews on the efficacy of anti-dementia medications including Cochrane-Reviews, from conclusions of national authorities like National Institute for Clinical Excellence (NICE, United Kingdom) and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Economics in Public Health, IQWIG, Germany) and from various national and international treatment guidelines (last guideline included was the German so called S3-Guideline "Dementia" of the Association of Scientific Medical Societes in Germany, 11/2009). The keywords were (dementia or Alzheimer or FTD, Pick's disease, frontal lobe dementia, semantic dementia, or vascul* or LBD and therapy and/or guideline).

This review considers different dementia populations and subjects from both community and institutional settings. Subjects in the studies had to be >18 years of age. This guideline includes pharmacologic treatment considerations for patients with Alzheimer's disease, vascular dementia, DLB, and fronto-temporal dementia. For the most part, when referring to Alzheimer's disease within the context of treatment, we are referring to probable or possible Alzheimer's disease or dementia of the Alzheimer's type, as diagnosed by NINCDS-ADRDA criteria (McKhann et al. 1984), or DSM-III-R or DSM-IV

criteria (American Psychiatric Association 1994). Vascular dementia refers to NINCDS-AIREN criteria (Román et al. 1993), including dementia occurring soon after a stroke, multi-infarct dementia as defined by DSM-III-R and DSM-IV (American Psychiatric Association 1994), and chronic leukencephalopathy. Dementia with Lewy Bodies is based on the Newcastle criteria McKeith criteria (McKeith et al. 2005), fronto-temporal degeneration to Lund-Manchester criteria (Neary et al. 1998). For the diagnosis of mild cognitive impairment (MCI), each study tends to construct its own set of criteria, but those are mostly based on Mayo criteria (Petersen 2004) with more or less variation (Anonymous 1989; World Health Organization 1992; American Psychiatric Association, 1980, 1987, 1994, McKhann et al. 1984; Roman et al. 1993; Petersen 2001; Graham et al. 1997; Graham et al. 1996; Folstein et al. 1975; Hachinski et al. 1975). 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 the diagnostic criteria described in Table III.

The potential for risk, or adverse events, was an important component to consider with respect to efficacy. The Jadad scale for quality (Oremus et al. 2001) does not take into account factors associated with adequate collection and reporting of adverse events as detailed by (Ioannidis and Lau 2002). Therefore, a summary checklist was used to determine the potential quality in the collection and reporting of adverse events.

Meta-analyses and guidelines

Scientific articles bear a high potential of methodological pitfalls. The reviewer system does only detect a minor number of faults in a publication. Even if rigourously evaluated many conclusions of studies remain arbitrary (see Excursus section). Thus, it is important to make the basis of conclusions transparent. In meta-analyses, these problems are even greater. Rosenthal and diMatteo (2001) and Möller and Maier (2007) have described the advantages and disadvantages of meta-analyses. In most meta-analyses the reviewer or reader must trust in the veracity of the content. Thus, meta-analyses are not transparent and they may, or may not, be scientific. Most guidelines include both articles and meta-analyses, making it difficult to determine the overall quality of the data. The present guideline of the WFSBP seeks to overcome this methodological flaw by reference to the underlying data base. For anti-dementia drugs the underlying database is attached. For NPS, the underlying database is described by Gauthier et al. (2010).

To double check flaws and shortcomings of studies, meta-analyses, Cochrane reviews, guidelines and independent reports are useful and were used. The cues on flaws and shortcomings in studies were used to optimize the selection of studies. For the studies included, tables for each intervention summarise the key data (see online Tables 1–10 and the resulting overview in Table VII). A list of studies excluded due to pitfalls and failures is not given but can be found in Cochrane reviews, guidelines and independent reports.

The field of dementia in medicine is a research area with a leading highly sophisticated methodology. The following differentiated excursus exemplarily will describe a part of the aspects that determine the outcome of studies not only in dementia.

Excursus: Methodological aspects of clinical trials in dementia

Study design

In clinical research on dementia treatment there are neither uniformly accepted criteria for disease progression nor a consensus regarding the magnitude of clinically important changes (Whitehouse et al. 1998; Rockwood and McKnight 2001). With respect to the therapeutic aims stated above, the practical consequences of these unresolved issues are that the same efficacy variables have been used to both show evidence of symptomatic benefit and demonstrate the effects on disease progression. Thus, the design of a clinical trial (rather than the outcome) is critical to demonstrating which of these two therapeutic outcomes (symptomatic benefit or delay in progression) is being achieved with the pharmacological agent (Leber 1997). Irrespective of which therapeutic goal is targeted by the pharmacological agent, the lack of consensus on these two issues has even more important implications when considering the definition of "efficacy". To base efficacy solely on statistical significance has long been recognized as problematic. A clinically relevant pharmacological treatment is seen as one that makes a "real difference", where the change is both relevant and important to the patient or to their families. This shows the difference between clinically significant (relevant and important) versus statistically significant (associated with probabilities), where the latter determines that the results are not due to chance or confounders. Moreover, a clinically important change will vary depending on whether importance is defined from the patient, family caregiver or clinician perspective. Clinically meaningful change reflects a different level of "significance", which may require a consensus among experts within the field to establish what magnitude of change is

regarded as important (Rockwood and McKnight 2001).

Accepting the criteria of the SIGN50 group (Wells et al. 2008) requires acceptance that between groups the only difference allowed as a pivotal outcome is the treatment under investigation. Comparing different trials requires the same restriction. However, RCTs fulfilling the inclusion criteria differ in many aspects (for instance age, stage of severity, diseases included, selection of patients, spectra of symptoms). Each of these aspects can be divided into a number of subcategories. Division into categories does not follow a common rule (for instance by using the same categorical meassure to assess the stage of severity). This situation becomes more complex when factors like doses of drugs used in a trial form new categories. The resulting picture can best be described as a multidimensional grid with at least three axes: diagnostic group, stage of severity, age of patients. Studies cover only a small part of the number of possible "study-boxes". In most of the boxes no study or only one study is presently available. So verification of the first result is often missing. This limits the possibility of a generalisation of the results to more areas than the one covered. For every area of interest, the multidimensional grid would have to be replicated. Although some studies include several outcome criteria the number of criteria differs. This leads to an unmanageable number of possible studies (for instance in measuring cognition, behaviour, activities of daily living, clinical impression etc.). For an evaluation, the conservative strategy of dimensional boxes would limit possible statements to a very narrow part of medical treatment. To allow for exact statements, studies in every box would be needed. Due to limited economical as well as scientific resources, it will be impossible to run the possible number of studies. Thus, strategies to reach conclusions on areas that are not precisely covered have to be accepted. One solution could be to permit conclusions based on age groups that were far removed from the mean age of the available studies and, thus, were only investigated in a smaller number of patients ("extrapolations", Oxford Centre for Evidence Based Medicine 2009).

A second source of study diversity stems from the particular tests employed. In all areas apart from cognition there is no standardized procedure or test and the validation of the tests is in an evolving stage (for instance the version of ADAS-cog used differs from study to study in the method of item administration or even in the number of items used). For rater training, no common rules are described. This means, if studies are comparable in the inclusion categories and more than one tester fills in a box incompatible test results might make a comparison or verification almost impossible.

A third major source of diversity results from different developments in the group of patients investigated. This is demonstrated by the alteration of test values of the placebo group that may have worsened dramatically or conversily improved after a 6 month trial period, for instance Kanowski et al. (1996) in comparison with Corey-Bloom et al. (1998). The rate of progression might also have had an effect on the study outcome, explaining these divergent results.

Relevant efficacy

The United States Food and Drug Administration (FDA) has established criteria for efficacy of antidementia (specifically for AD) drug interventions (Leber 1990) which require the following: (1) a double-blind, placebo-controlled trial, (2) subjects who meet established criteria for AD, (3) sufficient length of follow-up to appreciate a meaningful effect of the drug on cognition, and (4) a clinical change of sufficient magnitude to be recognized by a clinician. In establishing these criteria, it was assumed that the outcome measuring cognition was the primary change of interest, and that the global clinical evaluation would mirror the changes in the primary variable (Rockwood and Joffres 2002). In 1997, the European Medicine Evaluation Agency (EMEA) issued new guidelines that incorporated two new concepts for the treatment of AD (European Medicine Evaluation Agency (EMEA) 1997). Firstly, the EMEA guidelines suggested a measure of functional abilities in addition to a global measure, and noted that behavioural outcomes were important from a clinical perspective. Secondly, a definition of "responders" should be included in all trials, such that the degree of improvement in their cognition (or stabilization) was pre-specified. Nevertheless, these approaches with up to three criteria do not represent the symptom spectrum of dementia and moreover, do not cover other factors that also might contribute to the evaluation of a drug (i.e. quality of life, institutionalization, mortality, time spent caring etc.).

Moreover, the magnitude of the change reflecting a clinically meaningful improvement was not specifically stated in any of these guidelines (Table IV). Sufficient magnitude of the change would reflect a clinically important difference, and this would vary with the type of outcome selected. Several authors have attempted to define "clinically" relevant change. Gutzmann et al. (2002) developed an Efficacy Index Score (EIS), which is a checklist that combines dropout as well as the relevant improvements individually across three levels of assessment (cognitive function,

Table IV. Methods proposed to determine the outcome of clinical studies.

Author	Gutzmann et al. 2002, EIS	Mayeux and Sano 1999	Burns et al. 2008
Dropouts	Evaluating dropouts	percent of dropouts related to adverse events	
Cognitive function	Improvement of cognitive function	percent of the change in the treatment group relative to baseline (corrected for any change in the placebo group)	Improvement/stabilization/less than expected decline by < or = 2 or < or = 4 or < or = 6 points on the ADAS-cog.
Other domains	Improvement of activities of daily living		plus one other domain
Global function	Improvement of global function in cognition		Improvement or improvement/ no change in global response

activities of daily living and global function). Although, this summary score has not been validated relative to other traditional outcomes, it does present a unique example of determining efficacy in the context of anti-dementia drug interventions. Mayeux and Sano (1999) in reviewing drug interventions for dementia, evaluated efficacy as a percent of the change in the treatment group relative to baseline (corrected for any change in the placebo group) and contrasted this with the percentage of dropouts related to adverse events. Disease progression was considered with respect to the outcomes of (1) time until death, (2) nursing home placement, (3) loss of ability to perform Activities of Daily Living (ADL), or (4) severe dementia. In the context of clinical trials seeking to establish efficacy of pharmacological interventions, the latter outcomes may be problematic to ascertain. For a clinically relevant change, Burns et al. (2008) introduced cut-off criteria. None of the methods covers the whole spectrum of a dementia. The methods used determine and limit the interpretability of results. However for the patient suffering from a disease that progressively worsens, as long as the opposite is not demonstrated every improvement should be defined as clinically relevant (for ethical considerations see Katona et al. 2009).

Measuring efficacy with tests

EMEA guidelines acknowledge that no single test encompasses the broad range of disease characteristics associated with AD; nor has there been convincing evidence that an ideal (or reference) instrument exists to capture cognitive, behavioural, functional, or caregiver status (European Medicine Evaluation Agency (EMEA) 1997). Given the current state of research on outcome measures used in dementia trials for determining efficacy, a further dilemma is at hand. Ideally, all outcomes used to evaluate efficacy should have demonstrated acceptable psychometric properties, such as reliability, validity (construct), and responsiveness. The literature evaluating outcome measures in dementia trials suggests that most instruments have some limitations or at least more data are required to establish the properties for acceptability of the scales. However, since none of the presently used outcomes has been accepted as standard, the selection of the most appropriate outcome is arbitrary. Similarly, establishing a rationale to exclude studies based on a specific type of outcome measure would also be arbitrary. To minimize measuring failures, the degree of validation should be taken into account (i.e. objectivity, test-retest reliability, inter-rater reliability, construct validity, convergent validity, scope of application – for instance stage of severity, norm values available for the group of interest, defined sensitivity to detect change).

Rater training. For assessing test values, experienced raters are needed. Unfortunately, there is no standardised rater training available. If ever mentioned, studies merely state that there was rater training. This methodological flaw leads to a low inter-rater-reliability and poor test-retest-reliability. It increases the probability that an existing efficacy will not be detected.

Limitations of tests. Moreover, frequently used outcome measures have limitations such as bottom and ceiling effects, low sensitivity, and poor objectivity that undermine their validity. Some aspects of the most often used scales have even more influence on the interpretability of results.

To measure cognition, the Alzheimer's Disease Assessment Scale-Cognitive Section is used (ADAS-cog, Rosen et al. 1984). A basic quality aspect of a test is that it will be the same test in every study (example: if an inch is used, it should always have the same length). Yet, in most studies using the ADAS-cog different items are used. Due to manufacturing problems with the object naming task, it is not possible to use the same set of objects. As a result in some studies pictures of objects are used.

Moreover, the length of the test varies between 11 and 13 items also influencing results. Nevertheless, Rosen demonstrated that a decline of 1.28 points occurred within 12 weeks, a decline of 3.5 points within 6 months, and Stern et al. (1994) showed a decline of 9–11 points by 1 year. However, so far such alterations are not seen in the placebo groups of drug studies. After 6 months, in placebo groups of methodologically sufficient studies, the mean points of alteration lay between an improvement of 1.6 points and a worsening of more than 4 points. Without further explanatory statement for study duration of half a year, the magnitude of "relevant benefit" on the ADAS-cog was set as 4 points at endpoint in treatment over placebo (Food and Drug Administration 1989). Most of the studies demonstrate a mean improvement of below 4 points. It is self-evident that the decline will depend on the stage of a patient at the beginning of the evaluation. Thus, the real decline might have a much higher variability. The characteristics of the natural history of AD and other dementia types are best derived from longitudinal studies. However, the natural history of AD itself shows an enormous heterogeneity. This diversity of the natural history of disease has a negative impact on comparisons of drug efficacy across trials (Demers et al. 2000).

The Mini-Mental-Status-Examination (Folstein et al. 1975) has even more flaws. Many different versions are used leading to different results (Kaiser et al. 2009). To detect early stage of dementia, the sensitivity is as low as 20% (Blessed et al. 1991; Ihl et al. 1992, 2005; White et al. 2002; Wind et al. 1997). To measure the course of the disease as well as treatment effects, it is not precise enough (Clark et al. 1999). The recommendation is not to use it (Grade 1, Wilcock et al. 1994). The high variability of the MMSE makes finding efficacy more difficult. Bottom and ceiling effects as well as low consistency and curvilinear relations to severity over the course of the disease accompany the tests.

Measuring other variables like behaviour might be even more difficult. Symptoms occur and disappear in the natural course of the disease and the relation to the stage of severity is variable. Due to low validity, results concerning activities of daily living (ADL), quality of life and clinical global impression have to be interpreted with much more caution. Further, measures of these variables are obtained by proxy i.e. from reports from caregivers whose accuracy may be variable.

Problems of alternative measures. To overcome disadvantages of poorly validated tests, measuring mortality and time to nursing home placement are recommended (IQWiG 2007). These parameters are also arbitrary. For instance depending on the actual symptoms, nursing home placement can be seen as a positive as well as a negative outcome.

Presently, we lack generally accepted designs to test drugs that would modify the underlying disease (compared to attenuating the clinical symptom course). Therefore, the regulatory authorities such as EMEA and FDA have expressed an increasing interest in the development and use of potential surrogate markers of disease modification in secondary preventive trials on AD and risk stages of AD (Broich 2007). Biomarkers derived from CSF, blood or neuroimaging might play an important role in this respect. These markers will only be useful if applied in combination with clinical and neuropsychological measures of change, but might particularly be helpful to discriminate symptomatic from disease modifying effects. Nevertheless, as long as we do not know the cause of the underlying diseases the interpretations of biomarkers remains difficult.

Statistical aspects of evaluating trials

To exclude unwanted intervening variables, studies need to be carfully designed. Failures are observed in design and methods and statistics (Altmann 1994). A number of factors may prohibit any conclusion being reached. However, reviewers do not detect the failures, even with training (Schroter et al. 2008). Thus, improving the quality of reports has been recommended (Hopewell et al. 2008; Zwarenstein et al. 2009).

Especially in dementia trials, the JADAD scale (Jadad et al. 1996) or the CONSORT questionnaire (Moher et al. 2001) will not cover all relevant criteria. The "SIGN 50" (Wells et al. 2008) meets the most important aspects. However, it asks for a deep understanding of methods and details of a study. Moreover, inter-rater-reliability and validation data are lacking. A selection of important factors to look for is summarised in Table V.

Many other factors are discussed but the possible size of an effect is rarely defined. Determining efficacy in dementia trials evaluating pharmacological interventions may vary depending on the selection of the analysis type. In general, the types of analyses of primary data in trials fall into two main categories: (1) intention to treat analyses (ITT) with the method of 'last observation carried forward' (LOCF) to substitute for drop-outs, and (2) observed case (OC) or completed trial (CT). The advantages of ITT over OC analyses have been well explained (Fergusson et al. 2002), however, the LOCF method to replace

Table V. Examples of factors limiting conclusions in dementia trials.

Failure	Limited conclusions because of
Power too low	An existing effect might not be found
Heterogeneous groups	An existing effect might not be found
Groups differ in more than the variable investigated	Intervening variable occurs
Randomization inadequate or not done	Intervening variable occurs
Blinding inadequate or not done	Intervening variable occurs
Diagnostics do not follow the international criteria	High variability
Unknown disease severity	High variability
Low number of patients per centre (i.e. < 4)	High variability
Unknown number of centres	Self-evident
Psychometric tests not valid	High variability
Limitations of a test not taken into account	Self-evident
No specified rater training	Measurement corrupted
Failures in statistical evaluation	Self-evident
Overestimation of failures	Self-evident
Missing α-adjustment	Pretends significance
Use of other anti-dementia drugs	Increases noise
Use of other psychoactive drugs	Increases noise
Differential attrition	Confounds results
Use of Last Observation Carried Forward	Overestimates effect of drug

drop-outs may not be the most appropriate in the case of a chronic progressive disease, where 'return to normal' is not the expected outcome, but 'worsening from baseline'. It is well recognized that non-compliance is not a random event; thus, ITT analyses should be used to base principal conclusions of efficacy (Pocock and Abdallah 1998). In the context of some anti-dementia drug therapies, where dropout rates due to adverse events in general and other non-compliance reasons may be high, the ITT analysis minimizes bias over the OC analysis and the potential for type I errors when considering treatment efficacy. However, the ITT/LOCF analysis does tend to favour treatment effects, if dropouts due to adverse events are more likely under active treatment and if the likelihood for favourable outcome is higher the earlier the last 'real' observation is made. Both conditions are generally true for anti-dementia drug therapies. Thus, the optimal analysis, when there is a large loss to follow-up, is to conduct the analysis both ways and look for consistency. However, compared to failures done in the trial itself flaws in the statistical analysis are happening ex-post-facto. This means, in contrast to failures made in processing the trial, failures in statistics can be minimised by recalculation and a more exact result will be possible.

The current designs of clinical trials do not allow for the collection of adverse events whose rates may generalize to the population as a whole. It is misleading to assume that drugs shown to be safe and effective in trials are safe and effective in all other circumstances (Lasagna 1998). The nature of pre-market clinical trials makes it difficult to evaluate the benefits of drugs for the entire population of potential users, as criteria restricting entry into the trial do not necessarily reflect dementia patients in general. By their nature, some adverse events are not easily anticipated, and therefore are not screened for in some trials. The implementation of pharmacovigilance systems attests to the need for further capture of potential adverse events not captured in trials. Adverse events may be hard to predict or anticipate and are captured only if a trial protocol was designed to measure these events. A limited number of standardized instruments exist to capture these events reliably. Unique to individuals with cognitive decline is the potential problem of validity of the self-report instrument. Subjectivity needs to be recognised for reports completed by the caregiver. Furthermore, many trials may be underpowered to detect adverse events with an incidence of 1/1000 and lower.

Flaws in the interpretation of results

To exclude "euphoric over-interpretations", acceptance of the conclusions and language of authors' reports needs care and caution (Gilstad and Finucane 2008).

Results

Clinical trials fulfilling the suggested methodological criteria are available for five drugs (Table VI). The five anti-dementia pharmaceuticals belong to three different substance classes, i.e. cholinesterase-inhibitors, NMDA-receptor modulator and phytotherapy. Donepezil, galantamine and rivastigmine

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 VII. Data of anti-dementia drug studies are compared. For details see data of attachment Tables 1–10.

Drug/ Parameter	Donepezil	Galantamine	Rivastigmine	Memantine	Ginkgo Biloba extract
Description					
	Derivate of piperidine and a selective and specific cholinesterase inhibitor.	Tertiary plant alkaloid obtained from the Caucasian snowdrop. For the treatment of dementia, it is manufactured synthetically.	Brain selective pseudo-irreversible carbamate type cholinesterase inhibitor.	Uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist modulating the glutamate receptor.	Standardised plant extract (EGb761) of the Ginkgo leave with a strong antioxidant capacity
Location of studies					
	6 USA 1 Europe 2 intercontinental.	2 USA, 1 Europe 3 intercontinental	1 USA 2 intercontinental	5 USA 1 UK 1 Europe 1 China 1 International.	2 USA 2 Ukraine 1 Bulgaria, 1 Germany
Funding					
	9 Vendor	5 Vendor 1 other sources	3 Vendor	9 Vendor	6 Vendor
Design					
Patients/study	28 to 818	285 to 978	678 to 707	252 to 548	94 to 513
Patients/ centre	6 to 67	4–19	?	6–11	5 to 51
Centres/study	?	33–93 One study did not name the number of centres.	?	42–65	4–44
Duration	6 month in 7 studies, 12 and 13.5 months	5 studies with 6 month,1 lasted 5 months.	24 month in Bullock et al. (2005) 6 month in the other studies.	16 to 28 weeks.	5 studies with 6 month 1 with 12 month.
Dose	Recommended dose is 10 mg/d. In the two eldest studies of Rogers et al. (1998) and Burns et al. (1999) a 5 mg group was included. In the study of Winblad a reduction to 5 mg was allowed when side effects appeared.	The dose most often investigated was 24 mg (all studies). 2 studies investigated also 32 mg, 1 16 mg and1 a prolonged release compound.	One study investigated 24 and 36 mg/d (B304, 1998). The two other studies compared a low dose group with 1–4 mg/d, with a medium dose group of 6–12 mg/d and placebo.	Recommended dose is 20 mg/d. In all studies the standard dose was 20 mg/d. Concomitant medication differed between studies.	Recommended dose is 240 mg/d. 2 studies investigated 120 mg/d 4 240 mg/d. Thus, evaluation has to be done depending on the dose.
Other aspects	Two of the studies (Tune et al. 2003 and Krishnan et al. 2003) defined neuroimaging parameters as main outcome explaining a relatively low number of participants	One study which collected data in 57 nursing homes must be observed separately. For the Tariot study, the number of centres is not available.			One 3-arm trial investigated Ginkgo biloba, donepezil and a combination of both. No significant difference was found.
Inclusion criteria					
	6 probable AD 3 possible AD Thus, two groups have to be evaluated separately. One study	5 probable AD 1 possible AD It is evaluated separately. The severity rating was assessed with the MMSE. The spectrum in 5 studies covered	3 probable AD exclusively. MMSE inclusion criterion was 10–26 in all three studies. Corey-Bloom et al. (1998) also assessed the GDS stage. Study	7 probable AD, 2 VD. An age of 50 and more years and severity groups between an MMSE score	6 probable AD or VD For inclusion in 3 of the studies, the NPI value had to be >4.The severity range of the patients was 9–26

(Continued)

Table VII. *(Continued)*

Drug/ Parameter	Donepezil	Galantamine	Rivastigmine	Memantine	Ginkgo Biloba extract
	investigating probable AD (Tariot et al. 2001) included patients in nursing homes. It also had to be observed separately. One of the probable (Seltzer et al. 2004) and one of the possible AD group (Gauthier et al. 2002 a, b) used an aberrant stage of severity (Table I). Studies with aberrant stage of severity also need separate evaluation.	10–25 points, i. e. GDS 3–6. As no staging was done in the studies GDS staging was estimated from MMSE score. The nursing home study of Burns et al. (2009) included patients with values of 5–12 points (i.e. GDS 6–7). The other studies used an additional criterion of a minimal ADAS-cog score of >11 (3 studies) or 17 (2 studies). Studies with a higher ADAS-cog criterion comprised more severe patients.	duration was 6 month. Data were collected in 22–94 study centres. Approximately, the mean number of patients per centre lay between 10 and 32.	of 3–23 were included (GDS 3–6 respectively).	in the MMSE (i.e. GDS 2–6). Studies did not allow accompanying anti-dementia medication as well as other psychoactive drugs. This qualifies for separate evaluation.
Patient characteristics					
	There was no difference in age of placebo and treatment groups. In one of the studies the mean age was at least 10 years higher than in the others (Mohs et al. 2001). This also qualifies for separate evaluation. The proportion of females investigated was 10 and more percent higher in two (Winblad et al. 2001, Gauthier et al. 2002 a, b) and ten percent lower in one study (Seltzer et al. 2004). The baseline values in the NPI between treatment and placebo group were comparable for three studies but not for the Tune et al. study (2003).	The mean age was 72–78 years in five studies and 84 in the Burns et al. study (2009). The female ratio was between 51 and 67 percent in 5 studies. In the nursing home study it was 81. Between treatment and placebo group in all patient characteristics no significant differences were observed.	For all groups, the mean age varied between 71 and 76 years. There were no significant differences between placebo and treatment groups.	The mean age lay between 72 and 78 years. The range of the female ratio was 48–73 percent. The mean MMSE score lies between 7.7 and 18.9 points. In the baseline values of three memantine studies there is a tendency for a worse NPI score. For the SIB and the ADL, no obvious difference occurred between treatment and placebo groups.	The mean age was between 63 and 70 for all but one study. In the Schneider et al. study (2005) the mean age was 10 years higher. There was no obvious difference between treatment and placebo groups. 54 to 84 % of the patients were female. No obvious difference occurred between placebo and treatment group. Between placebo and treatment groups there were also no significant differences in the other baseline parameters investigated.
Possible statement area (Studies are allocated to an area when the parameter named was investigated as primary efficacy variable. The tables named can be found in the attachement. Outside the statement areas no data are available (**Level F**).					
	An overview of the field that the studies cover is given in table 2. Tariot et al. 2003 is included although the place of recruitment was nursing homes. Groups with a mean age below 70 years were not investigated. One study in probable AD included patients with higher age. Severity levels differ between studies and between parameters investigated.	For further analysis, the studies were included in a grid of possible studies that was developed from the main areas of interest (table 4). By contrast to table 2, stage as well as age was not used as a criterion because all but one study investigated the same stage and the same age groups. This means that reliable conclusions can be drawn on age groups with a mean of 70–80 years and on stages 3–5 in the GDS and might only be extrapolated on a group with a higher mean age (Burns et al. 2009).	All shown rivastigmine studies investigated patients with the same diagnosis (probable AD), the same age group (mean 71–75 years, std. 8 years), severity stage (i.e. GDS 3–5) and duration (6 months).	Four memantine studies investigated cognition and ADL in probable AD patients with the same degree of severity (GDS 5–6, mean MMSE 7.8–11.8) and comparable mean age (72–78). Two studies investigated cognition and clinical global impression in VD. Three studies investigated cognition and clinical	For probable AD, VD and AD/VD with NPS data are available. Part of the studies investigated 120 mg others 240 mg. Data are available for cognition, behaviour, ADL and CGI. GDS 3–6 was included in the studies. The LeBars study had lasted 12 month all the other studies 6 month. None of the studies investigated patients with a mean age of above 79 years.

				global impression in probable AD with a severity stage of GDS 3–5 (mean MMSE 16.718.9). The heterogeneity of groups investigated limits the conclusions as well as unexplained extraordinary placebo group responses.	
Cognition					
Probable AD	Three studies investigated cognition in groups of patients with *probable AD* with a mean age in the seventies as primary outcome variable (Burns et al. 1999, Rogers et al. 1998, Seltzer et al. 2004). Disease severity varied between studies. Burns et al. (1999) covered the broadest sprectrum (CDR 0.5–2, GDS 2–5). Seltzer et al. (2004) excluded stage CDR 2, Rogers CDR 0.5. 3 studies showed a significant improvement in the ADAS-cog of 2.3–2.9 points in 6 month (placebo-treatment difference). The study of Seltzer et al. (2004) used a 13-item ADAS-cog. Although this version contains more points the mean difference was lower than in the other two studies.In the primary efficacy variable cognition the studies demonstrated superiority of donepezil over placebo (**Level B**). This holds true for the severity stages 0.5–2 in the CDR or 2–5 of the GDS respectively in age groups with a mean age between 70 and 79 years.In the high age group with probable AD of Mohs et al. (2001) also a	Four studies investigating cognition in probable AD found an improvement of 2.9–3.9 points in the ADAS-cog when comparing placebo and treatment group (Raskind et al. 2000, Tariot et al. 2000, Wilcock et al. 2000, Brodaty et al. 2005). In the nursing home study a significant improvement of 4.9 points was found in the SIB (Burns et al. 2009). In groups with probable AD and a mean age between 72 and 78 years, galantamine demonstrated efficacy (**Level B**). In one study, investigating patients with a mean age of 84 a comparable efficacy was found (Erkinjuntti et al. 2002; **Level B**).	Three studies B304 (1998, IQWIG data), Corey-Bloom et al. (1998) Rösler et al. (1999) in AD found a significant improvement of rivastigmine over placebo in patients with a mean age of 71–75 and a severity level of GDS 3–5 (**Level B**).	For the primary efficacy parameter cognition in moderate to severe probable AD, the studies 10116 (2006) and van Dyck et al. (2007) could not find any significant result. For the same parameters, the results of the Cummings et al. study (2006) were significant and so were the results of Reisberg et al. (2003). Thus, the results of the Memantine studies in probable AD on cognition are inconclusive. When severity was mild to moderate 2 of three studies could not find significance (Bakchine and Loft 2007, 2008, Porsteinsson et al. 2008). However, study groups differed in the acceptance of concomitant medication and unexplained extraordinary placebo group reactions. A recent secondary analysis confirmed superiority of memantine in AD compared to	Four of five studies investigating cognition found a significant superiority of treatment over placebo Only Schneider et al. (2005) could not replicate the findings. However, in a subanalysis of patients with NPS a significant improvement was found too **(Level B).**

(Continued)

Table VII. *(Continued)*

Drug/ Parameter	Donepezil	Galantamine	Rivastigmine	Memantine	Ginkgo Biloba extract
	significant improvement of 2.1 points in the MMSE was seen. This underlines efficacy in a group with higher age (**Level B**). Mohs et al. (2001) as well as Winblad et al. (2001) also found superiority of the treatment group over placebo group after a longer investigation time of 13.5 or 12 month duration (**Level B).**			placebo (Ferris et al. 2009, **Level D**).	
Possible AD	In the primary efficacy variable cognition the study of Winblad et al. (2001) demonstrated superiority of donepezil over placebo (**Level B**).	A single study demonstrated superiority of treatment over placebo. It demonstrated a mean improvement of 2.7 in the ADAS-cog (Erkinjuntti et al. 2002). (**Level B**)	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).
VD	For vascular dementia, 3 studies, demonstrated superiority of donepezil over placebo (Black et al. 2003, Wilkinson et al. 2003, Roman et al. 2010; **Level B).**	No data (**Level F**).	No data (**Level F**).	Studies investigating VD found superiority of Memantine over Placebo in cognition. Thus, in VD Memantine is superior to placebo. (**Level B**).	Data on VD in the four studies investigating VD favoured significantly the ginkgo biloba extract compared to placebo (**Level B**).
Others	No data (**Level F**)	For groups with higher stages of severity no data are available (**Level F**).	No data (**Level F**)	No data (**Level F**)	For groups with older age, data are inconclusive (**Level D)**.
Behaviour					
Probable AD	No data (**Level F**)	Tariot et al. (2000) found significant superiority of galantamine over placebo in patients with a mean age of 76 years and GDS stage 3–5. In a pooled analysis this finding was supported (Cummings et al. 2004) (**Level B**)	No data (**Level F**)	When data are pooled, a significant improvement can be demonstrated (Gauthier et al. 2008, **Level B)**.	Two studies investigated behaviour with the NPI as primary efficacy parameter. Both found a significant superiority of treatment over placebo (Napryeyenko et al. 2007, Ihl et al., 2010, **Level B**).
Possible AD	Two studies included the NPI to measure behaviour as primary efficacy parameter. Gauthier et al. (2002 a, b) found a significant superiority of treatment over placebo in their trial. One study included patients from nursing homes (Tariot et al. 2001). This study could not find a significant difference between treatment and placebo treatment. Thus,	Erkinjuntti et al. (2002) found significant superiority of galantamine over placebo in patients with a mean age of 78 years and GDS stage 3–5(**Level B**)	No data (**Level F**)	No data (**Level F**)	No data (**Level F**)

	no reliable conclusions on the efficacy on behaviour can be drawn (**Level D**).				
VD	No data (**Level F**)	No data (**Level F**)	No data (**Level F**)	No data (**Level F**)	Same as probable AD **Level B**).
Others	No data (**Level F**)	For other age groups and higher stages of severity no data are available (**Level F**).	Two RCTs in Lewy body dementia had measured behaviour with the NPI as primary efficacy variable and found a significant improvement with rivastigmine compared to placebo (McKeith et al. 2000, Wesnes et al. 2002, **Level B**).	No data (**Level F**)	No data (**Level F**)
Activities of Daily Living					
Probable AD	Only results of secondary efficacy analyses exist. Two of the studies show improvement, two do not. Thus for ADL, efficacy of donepezil is inconclusive (**Level D**).	Three studies investigated ADL as primary efficacy variable (ADCS: Tariot et al. 2000, Burns et al. 2009; DAD: Wilcock et al. 2000,). Tariot found a significant improvement that was not observed in the Burns and the Wilcock study. Thus, no reliable conclusions on the efficacy of galantamine on ADL in the age group of 70–80 years and in stages 3–5 in the GDS can be drawn (**Level D**) For other age groups and stages no data is available (**Level F**).	Two of three studies measuring ADL as primary efficacy variable showed a significant improvement in AD in doses above 6 mg per day **(Level B)**. Higher or lower doses did not show a significant effect **(Level E)**.	For the primary efficacy parameter ADL in probable AD, the studies 10116 (2006) and van Dyck et al. (2007) could not find any significant result. For the same parameters, the results of the Cummings et al. study (2006) were significant and so were the results of Reisberg et al. (2003). Thus, the results of the Memantine studies in moderate to severe probable AD on cognition are inconclusive (**Level D**).	ADL were investigated in 5 studies (Kanowski et al. 1996, Le Bars et al. 1997, Schneider et al. 2005, Napryeyenko et al. 2007, Ihl et al., 2010). All but the study of Schneider et al. found a significant improvement under Ginkgo compared to placebo **(Level B)**.
Possible AD	No data (**Level F**).	Erkinjuntti et al. 2002 found a significant improvement. (**Level B**)	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).
VD	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).	Same as probable AD **(Level B)**.
Others	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).
Clinical Global Impression					
Probable AD	Two studies used the CIBICplus scale as primary outcome parameter in probable Alzheimer dementia and	Clinical Global impression as primary efficacy parameter was investigated in three studies (Raskind et al. 2000, Tariot et al. 2000, Wilcock et al.	Rivastigmine was significantly superior to placebo in the two studies investigating Clinical Global Impression in probable	2 studies in mild to moderate AD could not demonstrate superiority of Memantine one did.	Two of three studies investigated clinical global impression as primary efficacy variable. Only Kanowski et al. (1996)

(Continued)

Table VII. *(Continued)*

Drug/ Parameter	Donepezil	Galantamine	Rivastigmine	Memantine	Ginkgo Biloba extract
	severity stages between 0.5–2 CDR (2–5 GDS). Both found a significant improvement with treatment compared to placebo (**Level B**). For patients with more severe stages, no data are available (**Level F**).	2000). All three studies found significant superiority of galantamine over placebo (**Level B**).	AD (Corey-Bloom et al. 1998, Rösler, 1999; **Level B**).	For clinical global impression. Data are inconclusive (**Level D**).	could demonstrate superiority over placebo. Le Bars et al. (2000) and Schneider et al. (2005) failed to replicate the finding. For clinical global impression, no superiority resulted **(Level E)**.
Possible AD	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).
VD	Black et al. (2003) and Wilkinson et al. 2003 found an improvement, Roman et al. (2010) could not find an improvement (**Level D**).	No data (**Level F**).	No data (**Level F**).	2 negative studies (**Level E**)	Same as probable AD **(Level E)**.
Others	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).	No data (**Level F**).
Further Parameters					
	No data (**Level F**)	No data (**Level F**)	No data (**Level F**)	No data (**Level F**)	No data (**Level F**)
Combination studies and comparability					
	A three armed study of Yancheva et al. (2007) in 94 patients showed improvement of a standardized Ginkgo extract, donepezil and a combination of both after 6 month compared to baseline values. With this size of groups no difference between treatments was observed. This does not exclude every possible difference between treatments. However, when more patients are needed to demonstrate significant differences this means that an ever existing statistical difference would be smaller (**Level C1**). Due to different rates of drop outs, data of the comparison study between Donepezil and Rivastigmin of Bullock et al. (2005) are inconclusive **(Level D)**.	Porsteinsson et al. (2008) found no additional effect of a combination therapy with memantine. Dantoine et al. (2006) reported a positive effect of this combination. Results of a further study of memantine and galantamine are announced (Kornhuber et al. 2009). So far data are inconclusive (**Level D**).	See Donepezil **(Level D)**.	Memantine was investigated in combination with cholinesterase inhibitors in four studies with heterogeneous groups and contradicting results (Cummings et al. 2006, Dantoine et al. 2006, Tariot et al. 2004, Porsteinsson et al. 2008, **Level D**).	For combination therapy and comparability see donepezil (**Level C1**).
Side effects/adverse events					
	Studies did neither uncover another rate of side effects than described in table 6 of the paper nor other adverse events.				

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 EGb761	None	None	None	None	None	None
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,

there was no additive effect from selegiline plus vitamin E, neither agent improved cognitive function (ADAS-cog) compared with baseline values, and those on drug did not decline less than those on placebo on these types of measures. Although epidemiologic data suggest that anti-inflammatory drugs may be protective against the development of AD, few anti-inflammatory drug trials have been reported. In one 6-month trial of indomethacin, stabilization of cognition was suggested, although the authors reported a 44% dropout rate. A 6-month trial of diclofenac for treatment of AD reported slightly slower decline (not significant) and a 50% dropout rate because of adverse events. Investigating celecoxib and naproxen natrium, the ADAPT trial failed to demonstrate any positive effect on cognition. There was weak evidence for a detrimental effect of naproxen and concerns with cardiovascular safety (ADAPT Research Group 2008, 2009).

A recent trial of prednisone for the treatment of AD was negative. Epidemiological studies suggest that estrogen may be protective against the development of AD, and from this observation, the possibility that it also might have a therapeutic effect in AD has been suggested. To date, two clinical trials examining the ability of Premarin® to slow the rate of decline in women with AD were negative. Since neither of these agents fulfils the requirements set out by the WFSBP task force, they are not considered as treatment options.

Future drug development

For the three main anti-dementia classes, new substances are under development (for instance ZT-1 as cholinesterase-inhibitor and Huperzine A as cholinesterase-inhibitor and phytopharmacon, MEM 1003 as NMDA-channel modulator). Due to the fact that we do not know the cause of the disease many other attempts are speculatively investigated. One particular area of focus has been to decrease the amount of plaques in the brain, e.g., by immunisation. Substances and immunisation was developed to clean the brain from plaques. However, there is an opinion that the brain may be cleaned of plaques but the disease remains unchanged (Holmes et al. 2008). An overview of new attempts to develop anti-dementia pharmaceuticals can be found by Riederer (2009). So far none of the attempts demonstrates a potential to cure or stop the disease. Thus, new approaches will have to show superior efficacy or at least fewer side effects.

Developing drugs to treat dementia was guided by hypotheses on the cause of dementia. To explain all the alterations of dementia an integrative theory has been developed by the Hoyer group (Hoyer 2002; Salkovic-Petrisic et al. 2009). The hypotheses were deduced from pathological, biochemical and pathophysiological alterations found in the brain of patients with dementia. For future drug development, this model could be useful.

Behavioral disturbances in dementia

Often dementia is accompanied by neuropsychiatric symptoms (Alzheimer, 1906). In the literature these symptoms are also addressed as behavioral problems or behavioral and psychological symptoms of dementia (BPSD) or neuropsychiatric symptoms (NPS). An overview of symptoms included in the definition is demonstrated in Table IX.

Different tests are used to measure neuropsychiatric symptoms. Initially the ADAS-noncog (Rosen et al. 1984), the Behavioural Pathology in Alzheimer's disease rating scale (BEHAVE-AD, Reisberg et al. 1987), the Cohen-Mansfield Agitation Inventory (CMAI, Cohen-Mansfield, 1986; Cohen-Mansfield and Billig, 1986) and the Neuropsychiatric Inventory (NPI, Cummings et al. 1994) were developed. A variety of new tests was published without demonstrating superiority over existing tests and scales. Various scales are currently used in different studies. The spectrum of symptoms covered by the various tests is not congruent. Moreover, definitions for the symptoms differ. Thus, when neurosychiatric symptoms are measured results will not always be comparable. Most frequently in recent studies the NPI has been used and recommendations as to how to use it published (Gauthier et al. 2010).

In a further step attempts were made to find symptom clusters to define specific syndromes. As an example using the NPI four syndromes were differentiated (Aalten et al. 2007, 2008):

- hyperactivity (agitation, aggression, disinhibition, irritability, aberrant motor behaviour, euphoria);

Table IX. Examples of neuropsychiatric symptoms in dementia ("Hyperactivity", "psychosis" and "affective symptoms" are seen as syndromes and not separately named here).

Agitation	Delusions	Aberrant motor behavior
Aggression	Hallucinations	Pacing and wandering
Disinhibition	Nocturnal confusion	Appetite change
Irritability	Tearfulness	Eating alterations
Eupohria	Repetitive activities	Uncooperativeness
Depression	Inappropriate activities	Behavior dangerous to self or others
Anxiety	Apathy	Fear of being left alone
Phobias	Personality changes	Alterations in sexual behavior

- affective symptoms (depression, anxiety);
- psychosis (delusions, hallucinations);
- apathy (apathy, appetite and eating abnormalities).

When more specific scales like the CMAI are used a more subtle differentiation may appear (Rabinowitz et al. 2005). However, the syndromes may allow for a more practical recommendation of treatment strategies.

Concerning frequency and appearance of symptoms several studies have been carried out. They show that frequency and severity of symptoms depend on the kind of symptom as well as on the stage of the disease (see reviews: O'Connor et al, 2009a,b; Gauthier et al. 2010).

Contributing factors to the development of neuropsychiatric symptoms (NPS)

Not all patients experience NPS and only a part of symptoms of NPS will affect a single patient. Besides pathology causing dementia further causative factors are discussed. The efficacy of anti-dementia pharmaceuticals is described above. However, causative factors of NPS partially differ from dementia causes. Thus, they need reference.

Biological factors. Dementia pathology affects the whole brain. The regional development varies between different types of dementia. Nevertheless, all symptoms may appear in every type of dementia at a point in time. From a biological point of view several associations of symptoms and biological alterations have been reported. Again syndroms were measured with several different tests. Thus, although symptoms are named identically they may mean different behaviours and the study results can not be compared easily. An overview of a selection of possible associations between biological and behavioural alterations can be found in Gauthier et al. (2010). So far for the different results, an integrative hypothesis is missing. It is not ruled out that the underlying pathology or cause of dementia will also determine the type of behavioral symptoms. However, using other scales than the NPI to investigate the effect of dementia subtype and severity, Thompson et al. (2010) found no significant difference between AD and VD. Before drug treatment of behavioural symptoms on a biological basis is taken into account some very frequent causes of deteriorations have to be ruled out.

Diseases and side effects of drugs as contributing factors. Somatic diseases and conditions as well as side effects of drugs given for somatic diseases contribute to behavioural symptoms. Anticholinergic side effects of a broad spectrum of drugs or side effects of corticoids are examples.

Psychosocial factors. Three psychosocial theories describe possible causes of NPS (Gauthier et al. 2010). The first theory, Progressively Lowered Threshold, deals with the neuron loss in dementia. Inhibitory neurons get lost at first. It is proposed that inhibitory neurons are lost first and this is leading to reduced stress tolerance.

The second theory describes unmet needs like hunger, thirst or missing attention as cause of NPS. Healthy individuals usually have capacities to satisfy the need. In dementia a loss of connections in the brain might prohibit the combination of perception, interpretation of a perception and necessary behaviour to achieve the solution.

Behaviour theory is the basis of the third possible explanation of NPS. For example screaming as a stimulus might lead to social attention. It would act as positive reinforcement and increase the probability of the appearance of screaming.

Environmental factors. Environmental factors also may influence the probability of NPS (i.e. darkness, superheating or supercooling, off odour, loudness).

Treatment of NPS in dementia

Defining evidence of treatment in environmental as well as psychosocial treatment will have to employ the same methodological considerations as in drug therapy. However, the absence of severe side effects may reduce the requirements for a recommendation. Nevertheless, several studies investigated these aspects (see Livingston et al. 2005; O'Connor et al. 2009a,b; Gauthier et al. 2010, for reviews). These evaluations are the basis for and determine the following conclusions.

Elimination of causal factors. At first, modifiable causal factors (see above) have to be identified and addressed. Thus, disease states or side effects will have to be ruled out. Often environmental factors may be changed easily. This may also hold true for needs like hunger and thirst. Other needs like social attention will require more specific psychosocial intervention.

Psychosocial intervention. To define the further procedure, after diagnosis of dementia all available caregivers should be seen by the practitioner (family

counsellor). All necessary information should be given. Moreover, possible support should be explained and a training on psychosocial aspects of caring should be recommended.

Drug treatment. Only when psychosocial intervention and exclusion of other factors fail may drug treatment be necessary. Exceptions may occur when the behaviour requires urgent attention such as dangerous aggression and drug treatment may need to be started in tandem with other measures. Treatment with anti-dementia drugs is seen as a standard therapy in dementia. The evaluation above has already described the effect of anti-dementia drugs on behaviour. For this and further drug therapy, Gauthier et al. (2010) additionally have published a "background paper".

Hyperactivity. To treat hyperactivity with drugs neuroleptics often are used. There are results that can be interpreted as a hint to use drugs like risperidone (Brodaty et al. 2003; Katz et al. 1999; De Deyn and Rabheru 1999, AD, PDD, VD, mixed dementia) and olanzapine (Street et al. 2000; Clark et al. 2001; De Deyn et al. 2004; Sink et al. 2005). In some nations quetiapine often is used. However, methodological problems like low study size limit the evidence of efficacy of quetiapine treatment (Tariot et al. 2006; Kurlan et al. 2007; Rainer et al. 2007; Zhong et al. 2007; Paleacu et al. 2008; Shotbolt et al. 2009, **Level F**). The risk of side effects of neuroleptics is comparable to other drugs in used this indication (Finkel et al. 2005). Nevertheless, neuroleptics are accompanied by a high rate of side effects possibly including an increased mortality rate (Haddad and Dursun 2008; Schneider et al. 2006; Sultzer et al. 2008). Moreover, the result of neuroleptic treatment often is a symptom shift leading to new unsolved problems like extrapyramidal syndromes, falls and fractures (Haddad and Sharma 2007; Kamble et al. 2008; Liperoti et al. 2007).

In the literature, the efficacy of benzodiazepines to sedate an individual is broadly described. However, the half-life of benzodiazepines is prolonged with increasing age. Frequent paradoxical reactions, muscle relaxation, respiratory depression and a potential for dependency limit their usefulness in hyperactivity. Withdrawal *symptoms* including delirium *are* common. As an example in the US from 1998 to 2005 benzodiazepines were responsible of 15.2% of drug-induced delirium hospitalizations (Lin et al. 2010). Falls and fractures are often associated with the use of benzodiazepines.

Lithium does not have a positive effect in AD (Hampel et al. 2009).

Anti-epileptic treatment with valproate is ineffective (Lonergan et al. 2004, Herrmann and Lanctôt 2007) although positive results from mice results are reported (Qing et al. 2008). By contrast, carbamazepine may be of benefit for the behavioural disturbances in dementia (Herrmann and Lanctôt 2007; Pinheiro et al. 2008; Warner et al. 2008). The recommendation is based on a series of studies of the Tariot group. Starting with an observational study in two patients with positive outcome (Leibovici and Tariot 1988) a preliminary study underlined the results (Tariot et al. 1994) that finally were supported in a randomized clinical trial (Tariot et al. 1998). A further analysis supported the results after a wash out period (Tariot et al. 1999). However, the spectrum of side effects of carbamazepine needs close surveillance (Table X) and studies on a possible efficacy of new substances with lower side effects like eslicarbazepine are so far not available.

Affective symptoms

Depression in dementia has been investigated in several studies. For fluoxetine and sertraline, studies could not demonstrate efficacy (Auchus and Bissey-Black 1997; Petracca et al. 2001; Magai et al. 2000; Rosenberg et al. 2010; Weintraub et al. 2010). For citalopram, efficacy is reported (Nyth and Gottfries 1990; Nyth et al. 1992) and it is recommended in the review of Herrmann and Lanctôt (2007). Karlsson et al. (2000) saw comparable efficacy of citalopram and mianserin in a further trial. Trazodone was investigated by two research groups. Lebert et al. found efficacy to treat behavioural symptoms in dementia in a pilot study in 1994 and in a double blind trial in FTD in 2004 (Lebert et al. 1994, 2004). Sultzer et al. (1997) also found efficacy in a double blind trial and in a secondary analysis they stated that mild depressive symptoms and agitated behaviour respond to trazodone treatment (Sultzer et al. 2001). However, there is a need for further studies.

Psychosis and apathy

For psychosis, practice treatment most often includes neuroleptics. However, side effects of these substances require specific caution (see above and Schneider et al. 2006; Gauthier et al. 2010). For efficacy of cipramil as an alternative treatment, an indication can be found (Pollock et al. 2002, 2007). For drug treatment of apathy, no RCTs were found. However, one RCT favors an individualized functional training program (Lam et al. 2010).

Table X. Overview of frequent side effects of pharmaceuticals used in the treatment of behavioural disturbances in dementia.

Generic name	Contraindications	Nausea/ gastro-intestinal	Cardio-vascular	Neurological	Others
Citalopram 10–20 mg in the morning	Simultaneous intake of MAO-inhibitors or pimozide. Severe disturbance of renal function	Nausea, obstipation, loss of appetite, diarrhoea,vomiting, gastro-intestinal complaints, vermehrter Speichelflussloss of weight, weight gain	Tachycardia, palpitations,	Tiredness, sleeplessness headache, tremor, try mouth, increased sweating, asthenia, agitation, anxiousness, nervosity, confusion, abnormal treams, disturbance of concentration, dysgeusia, paraesthesia, extrapyramidal symptoms, visual disturbances, tinnitus, yawning, rhinitis, pruritus, eczema, myalgia, arthralgia, dizziness, gestörtes Allgemein-befinden, apathia,	Reduced libido, female orgasm disturbance, impotence, disturbance of ejaculation, orthostatic hypotoniaurinary retention,
Trazodone 50 mg at night	Acute Intoxication withhypnotika, analg etics,psychopharmaca,carcinoid syndrome, alcohol intoxication, cardiac arrhytmia, Decompnsated cardio vascular insufficiency	Gastro-intestinal complaints	Cardiac arrythmia, orthostatic dysregulation	tremor, tiredness, dizziness, headache, confusion, sleep disorders, agitation, visual disturbances	Withdrawal syndrome, priapism
Risperidone 0, 25–2 mg in the morning	Hyperprolactinaemia independent of drug intake	Gastro-intestinal complaints, weight gain	Hypotonia, orthostatic dysregulation; stroke	Provocation of epileptiform seizures, extrapyramidal symptoms, disturbed gait and falls	Death
Olanzapine 2, 5 mg in the morning	Known risk of glaucoma	Weight gain, metabolic syndrome	QTc-prolongation Orthostatic hypotonia	Tiredness, extrapyramidal symptoms, disturbed gait and falls	Pneumonia, increased temperature, lethargia, erythema, visual hallucinations, incontince of the bladder
Carbamazepine 50–100 mg retarded at night	Hypersensitivity to tricyclic anti-depressives, history of bone marrow impairment or depression, atrio-ventricular block, acute intermittend porphyria, combination with MAO-inhibitors (14 days period without MAO-inhibitors before beginning of treatment), combination with voriconazol (no treatment effect)	None		Tiredness	Altered blood count, hyponatraemia, increased lever enzymes, many drug interactions (decreased blood level and increased risk of side effects)

Conclusions

Dementia diseases are an interdisciplinary challenge, where psychiatrists and neurologists have equal importance in the neuropsychiatric centers in the treatment of dementia. Multi-level guidelines consider the family doctors care as well as the requirements for specialized centers for dementia treatment.

In most cases, drug treatment with anti-dementia drugs preferably combined with non-pharmacological treatments may substantially provide benefits and improve quality of life in patients and their carers with this disorder. However, so far dementia can not be cured or arrested.

When neuropsychiatric symptoms appear, psychosocial intervention is the treatment of first choice. For efficacy of drug treatment in NPS, the evidence is limited. Moreover, possible side effects often prohibit the use of pharmaceuticals.

Treatment recommendations for Alzheimer's disease and other disorders associated with a dementia syndrome

The data based analysis (see Supplementray Tables 1–10 (available online) and Table VII in the text as well as Gauthier et al. 2010) considering the methodological aspects described let to the following treatment guidelines.

The use of anti-dementia pharmaceuticals

Prevention. For prevention under the age of 70 years, there are no data for donepezil, galantamine, rivastigmine, memantine and Ginkgo biloba extract (**Level F**). For prevention over the age of 70 years first hints of efficacy of Ginkgo biloba were found accidentally by Andrieux et al. (EPIDOS, 2003). One confirmation study with Ginkgo biloba extract with a low transition rate to dementia in both groups and insufficient drug intake rate failed to demonstrate efficacy (GEM, DeKosky et al. 2008). A second confirmation study presently becomes evaluated and first positive results were presented (GUIDAGE, Vellas et al. 2006; Ipsen, 2010, **Level D**). For other anti-dementia pharmaceuticals and for other types of dementia in both age groups, no data exist (**Level F**). Thus, for prevention anti-dementia pharmaceuticals so far cannot be recommended.

Methodological limitations of studies in the prevention of so called "MCI" do not allow conclusion on preventive effects. Thus, anti-dementia pharmaceuticals cannot be recommended in MCI.

Indication of treatment. For curing or arresting of AD or VD or any other type of degenerative dementias no drugs can be recommended.

For the symptomatic treatment of AD, donepezil, galantamine, memantine, ginkgo biloba extract, rivastigmine show a modest, over a limited time, effect in a part of the patients **(Level B)**. Donepezil, galantamine, rivastigmine show reasonable, memantine and ginkgo biloba extract less side effects **(Level B)**. For symptomatic treatment of AD, these pharmaceuticals can be recommended (**Grade 3**). For VD, in several nations anti-dementia pharmaceuticals are not licensed. However, the scientific data are also convincing and anti-dementia pharmaceuticals should be recommended too (**Grade 3**). For Lewy body dementia, rivastigmine can be recommended (**Grade 3**). For other drugs in Lewy body dementia and frontal lobe dementia, data are lacking. Nevertheless, treatment with anti-dementia pharmaceuticals should be a treatment option (**Level C3, Grade 4**).

Methodological inadaequatnesses prohibit a systematic recommendation of pharmaceuticals related to specific severity levels (see excursus **Level F**).

Selection of drugs. Every substance has its own efficacy spectrum and its own side effect profile (see Tables VII and VIII, **Level B**). For a patient, the individual symptom constellation and the probability of side effects and the stage of the disease should determine the selection of the drug (**Level C3, Grade 4**).

Dose. For treatment, the following target daily doses are recommended: donepezil 10 mg, galantamine 24 mg, rivastigmine 12 mg (rivastigmine patch 9.2), memantine 20 mg, Ginkgo biloba extract 240 mg (**Grade 3**). Side-effects may prohibit use of the recommended dose (**Level C3, Grade 4**).

Effect size. Over all substances the median improvement in 6 month is 2.3 points in the ADAS-cog-scale (**Level B**). This effect is classified as a modest symptom improvement over a limited time in a part of the patients.

Beginning and end of treatment, surveillance. The treatment should start after diagnosis with clearly defined treatment goals (**Level C3, Grade 4**). The end of treatment should depend on an individual decision (**Level C3, Grade 4**). It should be discontinued if there are significant adverse effects or after consensus with patients and relatives/caregivers/legal representatives (**Level C3, Grade 4**).

Patients should particularly be monitored for adverse effects in the first 6 weeks after commencing treatment or after dosage adjustment (**Level C3, Grade 4**). Patient status should be documented after 3–6 months of treatment at the highest tolerated recommended dosage (**Level C3, Grade 4**).

Any significant deterioration in the patient's condition should lead to a rigorous re-assessment of the diagnosis and a work-up on potential intercurrent disases, but not automatically to discontinuation of anti-dementia drugs. All patients on long-term treatment should be reassessed at least every 6 months (**Level C3, Grade 4**).

Combination therapy

There are findings showing that combination therapy of drugs with different modes of action might have a synergistic effect (**Level C**). With respect to the importance of the disease combination therapy should be a treatment option (**Level C3, Grade 4**).

Additional recommendations: vascular dementia

Risk factors for VD are high blood pressure, cardiac disorders, hematocrit over 45% and diabetes mellitus, which are also risk factors for stroke. Obviously, if underlying vascular disease or strokes are leading to dementia, any primary or secondary prevention of cerebrovascular disease would seem to be a reasonable therapy (Qizilbash 2002, **Grade 4**).

The most promising approach to VD is secondary prevention of cerebrovascular disease besides symptom management (**Grade 4**). Although there is evidence to support the use of aspirin to prevent stroke in patients, no stroke prevention trial has been confined to patients with VD (Rands et al. 2004). No unconfounded, randomized controlled trials of blood pressure reduction in established VD were found (**Level F)**.

Management of behavioural and psychological aspects of Alzheimer's disease and other disorders associated with dementia

For the following recommendations, it is assumed and recommended that treatment with anti-dementia pharmaceuticals is sufficiently done as recommended (**Grade 3**, see above).

When behavioural disturbances like hyperactivity or depressed mood accompany the disease possible other causes have to be ruled out (i.e. other diseases, physiological needs like hunger and thirst as well as psychosocial causes like missing attention and environmental factors like temperature and odor, **Grade 3**). Elimination of causative factors and psychosocial intervention are the treatment of choice (**Grade 3**).

When all attempts fail, drug treatment will be the last option (**Level C3, Grade 4**). However, the high rate of partially severe side effects should limit the use of drugs (**Level A, Grade 1**).

For the hyperactivity syndrome, there are indications that drugs like the following substances could be a last option when side effects are monitored, the dose is kept low and the duration of the treatment is as short as possible (**Level C3, Grade 4**): risperidone, olanzapine, quetiapine, aripiprazol, citalopram, trazodone and carbamazepine. In practice, the hyperactivity syndrome including for instance screaming and aggression often is accompanied by insufficient drug response (**Level C3**). Valproic acid as well as lithium should not be used (**Level E**). For depression, there is no RCT demonstrating that antidepressives do not work in dementia with depression (**Grade 5**). For psychosis, the same restrictions as for hyperactivity apply. For apathy, no data do exist (**Level F**).

General management principles for dementia

The physician in charge of the treatment and care of the patient should schedule regular follow-up visits (American Psychiatric Association 2002; Rosen et al. 2002). The purposes of planning systematic follow-up include (Waldemar et al. 2000):

- To ensure identification and appropriate treatment of concomitant conditions and of complications of the primary dementia disorder.
- To assess cognitive, emotional and behavioral symptoms.
- To evaluate treatment indications and to monitor pharmacological and non-pharmacological treatment effects.
- 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. Several further questions appear relevant for practice guidelines, but are as yet unresolved due to a lack of evidence.

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Supplementary material available online

The data base of RCTs that fulfilled the methodological criteria of the work group (Tables 1–10).