Dementia is one of the most common diseases of old age, affecting up to 20% of the population depending on age and diagnostic criteria. The most common form of dementia is Alzheimer’s disease (AD), which presents with a typical clinical course of symptoms of which each represents a possible target for therapy. Memory impairment at onset of clinical AD refers to episodic memory deficits. Correspondingly, at onset of clinical AD the hippocampus is affected with or without neocortical neuronal lesions. In human patients, this can be visualised by use of functional magnetic resonance imaging (fMRI). With the spread of disease, a wide spectrum of cognitive and behavioural domains are affected; anatomically, the disease spreads out from an initial affliction of the entorhinal cortex to the temporal, parietal and, finally, frontal cortex. The spread of disease can also be mirrored with detailed neuropsychological testing and imaging methods.

Acetylcholine is a major neurotransmitter in the hippocampus, and memory failure in ageing and AD is hypothesised to result from impairment of the cholinergic system. It has been shown that the primary lesion at onset of clinical AD lies within the hippocampus, where synaptic transmission is the major correlate for memory deficits; neocortical neuronal lesions may also be found. Results can be reproduced in transgenic models of the disease. Accordingly, a therapeutically induced increase of cholinergic neurotransmission is used to treat patients with Alzheimer’s disease. Improved hippocampal recruitment on cholinergic therapy can be portrayed by functional imaging even in subjects with very mild hippocampal deficits.

**Treatment Guidelines Issued by Medical Associations**

Several medical associations have issued recent guidelines on the treatment of AD, among them the German Neurological Association (DGN) in 2005 and the American Psychiatric Association (APA) in 2007. Unanimously, these guidelines recommend acetylcholinesterase inhibitors for the treatment of AD patients with mild to moderate severity without giving boundary scores in terms of scores on the mini-mental status examination (MMSE). Again unanimously, these guidelines recommend memantine for the treatment of moderate to severe AD. Very specifically, the DGN guideline comes to the conclusion that treatment should be started immediately on diagnosis of AD and that no evidence-based measurement tool for the assessment of decline under treatment is known. Therefore, cessation of therapy is recommended only on the occurrence of side effects or contraindications such as cardiac arrhythmias or bronchial asthma. On pronounced deterioration under treatment it is recommended that the antidepressa therapy be continued while looking for intercurrent diseases.

**Evidence-based Treatment of Dementia**

a report by

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Concerning the acetylcholinesterase inhibitors, the report comes to the conclusion that the three acetylcholinesterase inhibitors are efficacious for mild to moderate AD. It is summarised that all three substances are of similar efficacy. While fewer adverse effects were found to be associated with donepezil compared with rivastigmine, it is concluded that galantamine and rivastigmine are comparable to donepezil in terms of tolerability if a careful and gradual titration routine over more than three months is used. Concerning memantine, the authors come to the conclusion that memantine has a small beneficial effect at six months in moderate to severe AD and a small beneficial effect on cognition in mild to moderate AD. It is also concluded that memantine is well tolerated.

**Treatment Guidelines Issued by Independent Organisations**

The Cochrane Collaboration has repeatedly issued reports on the efficacy of the acetylcholinesterase inhibitors and memantine, most recently in 2006. Concerning the acetylcholinesterase inhibitors, the report comes to the conclusion that the three acetylcholinesterase inhibitors are efficacious for mild to moderate AD. It is summarised that all three substances are of similar efficacy. While fewer adverse effects were found to be associated with donepezil compared with rivastigmine, it is concluded that galantamine and rivastigmine are comparable to donepezil in terms of tolerability if a careful and gradual titration routine over more than three months is used. Concerning memantine, the authors come to the conclusion that memantine has a small beneficial effect at six months in moderate to severe AD and a small beneficial effect on cognition in mild to moderate AD. It is also concluded that memantine is well tolerated.

**Treatment Guidelines Issued by Institutes with Governmental Assignment**

In February 2007 the German Institut für Qualitätssicherung und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) issued an evaluation of acetylcholinesterase inhibitors for the treatment of AD. Overall, the conclusion was that the assessed inhibitors of acetylcholinesterase (donepezil, rivastigmine, galantamine) are effective in terms of cognition and activities of daily living in all assessed dosages (donepezil) or in a dose-dependent fashion (rivastigmine, galantamine). Moreover, it was concluded from the studies included in the IQWIG meta-analysis that proof of efficacy in terms of psychopathological symptoms had been shown for galantamine. All three substances were evaluated to have dose-related side effects. In the overall conclusion there was deemed to be insufficient evidence for differences in treatment efficacy for the assessed substances. The evaluation was concluded to be applicable for a treatment period of six months. No specific recommendations were made concerning onset of treatment, treatment monitoring or treatment cessation. An evaluation of memantine has not yet been issued. The recommendations of IQWIG are not binding for physicians in Germany and the final decision about reimbursement by insurance companies depends on a decision by another government agency.

The amended guideline of the National Institute of Clinical Excellence (NICE) of September 2007 comes to the conclusion that the acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) are a treatment option for patients with AD of moderate severity (MMSE score 10–20) only. It is recommended that only specialists in the care of patients with dementia (i.e. psychiatrists, including those specialising in learning disabilities, neurologists and physicians specialising in the care of the elderly) should initiate treatment. It is advised that treatment monitoring should include the MMSE, with cessation of treatment in those reaching a score of 10 or below. Within the given corridor of treatment it is advised to continue treatment as long as the drugs are considered to have a ‘worthwhile’ effect, taking into account the global,
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Discussion and Conclusion

Evidence-based medicine helps individual physicians to decide the best choice of treatment for individual patients. The results of double-blind, placebo-controlled studies and meta-analyses of these studies are considered best evidence regarding the objective appraisal of the efficacy of treatments. Based on these kinds of studies, licensing authorities such as the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) came to the conclusion that there is sufficient evidence to license cholinergic drugs (donepezil, galantamine, rivastigmine) and the antiglutamatergic drug memantine for the treatment of mild to moderate AD.

However, the discussion is supplemented by arguments about the ‘relevance’ of the effect for the individual patient. There are also limitations in gathering reliable information about the impairments, needs and preferences of patients with AD and their care-givers, especially with progressing disease and the resulting impairment of communicative capabilities on the part of the patient. The fact that impairments may fluctuate or may surface only under certain conditions is also explicitly discussed.

In the view of the author, ‘relevance’ or ‘clinical benefit’ cannot be defined in scientific terms, but rather represent a judgement on the worth of a treatment, or an assessment of its effect versus its expense; as such, they go beyond the principles of evidence-based medicine. Only on consideration of these additional judgement domains – i.e. beyond just ‘effectiveness’ – can tests to determine whether a substance should be applied set strict upper and lower boundaries. From an evidence-based medicine point of view there is insufficient evidence to propose such a procedure. From a scientific point of view, the test–re-test reliability of the MMSE25,26 and the variability of progression of disease in individual patients due to a multitude of internal (genetic background) or external (fluctuations of blood pressure, metabolism and fatigue; intercurrent subclinical diseases) reasons precludes the fixing of strict boundaries, and no grade I evidence supports the proposed procedure (see Figure 1).

In light of the lack of scientifically founded procedures, it thus needs to be concluded – based on several grade I studies and supported by biological and physiological considerations – that treatment with cholinergic drugs is indicated in subjects with mild to moderate AD and treatment with memantine is indicated in moderate to severe AD. Treatment needs to be continued as long as the main diagnosis of AD is still valid and no contraindications arise. How to proceed with treatment on transition from the moderate to the severe stages of disease is unsupported by systematic evidence at present and needs to be decided at the level of the individual patient. Cessation of any kind of specific antidementia therapy in advanced stages of disease does not rest on evidence-based data at present; any such decision needs to consider the specifics of each individual patient and his or her care-giver.