Clinical Medicine Insights: Therapeutics

EXPERT REVIEW

Cognitive Enhancers in Moderate to Severe Alzheimer's Disease

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Abstract: The treatment of moderate to severe Alzheimer's disease is reviewed with regard to mechanisms of action, pharmacokinetics, metabolism, safety/tolerability, and efficacy in reducing cognitive, behavioral/psychiatric, functional and global symptoms. The cholinesterase inhibitors donepezil, rivastigmine and galantamine and the *N*-methyl-D-aspartate receptor channel blocker memantine are moderately beneficial. Small improvements over a few months are followed by slowed mental decline. Concerning cognitive, functional and global functions, these drugs are similarly effective. Cholinesterase inhibitors also reduce apathy, memantine counteracts agitation and aggression. Serious adverse effects are rare with all four drugs. Cholinesterase inhibitors bear a risk for patients with cardiac diseases. Adverse emetic events are typical for oral formulations of these drugs, but less for rivastigmine transdermal patches. Other routes of administration and use of a galantamine prodrug are currently investigated. The superiority of combination therapies over monotherapies requires further support. Promising investigational drugs include the copper/zinc ionophore PBT2 and multifunctional hybrid molecules.

Keywords: Alzheimer's disease, Cu/Zn ionophores, donepezil, galantamine, memantine, rivastigmine

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Introduction

Alzheimer's disease (AD) is characterized by amyloid-β peptide (Aβ) toxicity, formation of amyloid plaques, hyperphosphorylation of *tau* and cytoskeletal tangles. The progressive, devastating neurodegeneration resulting from these changes cannot be halted by current treatments. The prevalence of AD is steadily increasing and expected to rise from about 25 to over 80 million patients worldwide by 2040.[1,2] Although various risk factors and several aspects of neurotoxicity have been identified that lead to losses of neurons and reduced connectivity, the etiology of this disease is not understood in terms of initiating alterations. The frequently read statement that the origins of AD are presumably multifactorial may be correct.[3–6] This would be in accordance with the multiplicity of risk factors. However, this assumption may somehow reflect our helplessness concerning the disease onset. Consequently, the approved treatments are, in their essence, symptomatic.

Even though current AD pharmacotherapies do not stop the progressing neurodegeneration, symptomatic treatments can moderately improve cognitive functions, memory and daily life, and attenuate disease-related behavior. A transient support of the patient's quality of life and the reduction of caregivers' burden must not be underrated.

Four approved drugs are actually in use, the cholinesterase inhibitors (ChEIs) donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®, Razadyne®), and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine (Ebixa®). Many other compounds are in preclinical or early clinical stages of investigation. The three ChEIs have been licensed for the treatment of mild to moderate AD (in the US, donepezil also for severe AD), whereas memantine has been approved for moderate to severe AD, with several deviations and limits by national regulations.

The use of ChEIs is based on the so-called cholinergic hypothesis.[6–9] This concept had been developed in accordance with early clinical and anatomical observations as well as pharmacological studies in humans and non-human primates. Impairments of memory and cognitive functions in AD were shown to be associated with a rather specific neuronal death in the main cholinergic output system, the basal forebrain, in particular, the nucleus basalis of Meynert and medial septal nuclei, and with corresponding degeneration in the diagonal band of Broca. These changes impair the cholinergic transmission to cortex and hippocampus. Moreover, central cholinergic blockade by scopolamine led to AD-like memory deficits, which were reversed by the ChEI physostigmine. The rationale of ChEI treatment is, therefore, to normalize cholinergic transmission by reducing acetylcholine (ACh) cleavage and thereby enhancing its concentrations in the synaptic cleft.

Neurodegeneration in AD is, however, not restricted to the cholinergic system and not to the areas mentioned. With regard to the complexity of central neurotransmission and multiple interactions arising thereof, functional deficits or excitotoxic alterations were observed with various neurotransmitters, such as serotonin, norepinephrine, dopamine, some neuropeptides and glutamate.[10] In AD, the glutamatergic NMDA receptor (NMDAR) is excessively stimulated, an effect that leads to Ca^{2+} overload and excitotoxicity.[11–14] As deduced from animal models and studies in transfected cells, these changes may result mainly from three causes, (i) a reduction in nicotinic ACh receptor-mediated inhibition of NMDAR activation,[15] (ii) direct activation of the NMDAR by Aβ peptide,[16] and (iii) indirect activation of the NMDAR by glutamate release from microglia exposed to Aβ.[17] Treatment with the moderately inhibitory, uncompetitive NMDAR antagonist memantine intends to prevent fatal overstimulations of this receptor and, thus, excitotoxic cell death.

In addition to the approved drugs, numerous investigational compounds have been developed for purposes of cognitive improvements in AD. Relatively few of them have reached the stage of clinical investigation. The strategies vary from targeting other neurotransmitter systems, attempts of reducing Aβ formation and toxicity to the use of multifunctional drugs. These multi-factorial hybrid molecules combine residues that interact with different binding sites of receptors or channels or contain an additional antioxidant moiety.

In contrast to the high number of these rarely investigated compounds, the approved cognitive enhancers have been studied in numerous clinical trials. Even the number of reviews would by far exceed the frame of an article of reasonable length. Several of the reviews and meta-analyses

published during the last years provide comprehensive information on design and outcome of the studies on donepezil,[18–37] rivastigmine,[18,20,23–25,29,32,33,37–45] galantamine,[18,20,23–25,29,32,33,37,46–51] and memantine.[14,21,30,39,52–65] As a bottomline, the approved drugs are capable of affording moderate improvements of cognitive and behavioral functions, but only for a limited period of time. This view has not changed during the last years. Therefore, this review will, instead of repeating what has been reported and summarized many times, primarily focus on recent publications, on new insights and developments.

Mechanisms of Action, Metabolism and Pharmacokinetic Profiles

Cholinesterase inhibitors

ChEIs aim to antagonize memory, cognitive and behavioral impairments by enhancing ACh concentrations in the synaptic cleft and, thereby, improving cholinergic neurotransmission. The apparently logical rationale of normalizing synaptic ACh signaling has, however, some physiological limits, which are rarely considered by clinicians. ACh levels vary within the circadian cycle[66,67] and, during night, also between sleep stages.[66–68] These functional changes have different consequences for memory and cognition. High levels of ACh, as supported by ChEIs, favor wakefulness, facilitate memory encoding and presumably also cognition. Low ACh concentrations, as occurring during slow-wave sleep, are required for consolidation of the declarative memory. Non-declarative memory consolidation is, however, favored during REM (rapid eye movement) sleep, during which ACh is elevated.[67] Donepezil was shown to increase REM sleep in AD patients.[69,70] Therefore, the pharmacokinetics of ChEIs leads to different consequences concerning declarative memory consolidation. Donepezil, which is more slowly absorbed (t_{max} = 3–5 h), but even more slowly eliminated ($T_{1/2}$ = 50–80 h; 100% bioavailability),[67] should rather disfavor this type of consolidation. Under this aspect, the more rapidly acting rivastigmine (t_{max} = 0.5–2 h; $T_{1/2}$ = 0.6–2 h; bioavailability 35%–40%)[67] may appear to be of advantage, but only if it is orally administered and not via transdermal patches. The pharmacokinetics of galantamine is of an intermediate type (immediate release: t_{max} = 0.9–2 h; $T_{1/2}$ = 7–8 h; prolonged release: t_{max} = 4.4 h; $T_{1/2}$ = 8–10 h; 100% bioavailability for both formulations). For this reason, appropriately timed galantamine may be easily adapted to the circadian cycle of cholinergic activity (what has rarely been done),[67] whereas this is not possible with donepezil or rivastigmine capsules. Rivastigmine transdermal patches, from which the drug is much more slowly absorbed (t_{max} = 8.1 h), generate an almost constant plasma level over 24 h.[39,44,71] However, the circadian timing may become less relevant as soon as circadian clocks, timing of sleep and sleep architecture are severely impaired in the course of disease progression.[67,72]

The considerable $T_{1/2}$ differences between ChEIs are explained by protein binding and elimination pathways. In the circulation, donepezil is to more than 95% protein bound[19] and, therefore, slowly eliminated by hepatic CYP 2D6 and CYP 3A4 monooxygenases. Less than 40% of rivastigmine are bound to plasma proteins, which contributes to the short action of the oral formulation.[73] The compound is, in part, hydrolyzed by acetylcholinesterase, but excreted largely unmetabolized[74] or as a sulfate conjugate.[73] Because of an absent liver metabolism, drug interactions at the CYP level do not occur. Only a small fraction of galantamine is bound to plasma proteins (18%).[74] Renal and hepatic (by CYP 2D6 and CYP 3A4) pathways contribute to the elimination of this drug.[74]

The inhibitory actions of ChEIs are not identical. Donepezil is a selective, reversible inhibitor of acetylcholinesterase (AChE), which blocks the enzyme's active center. Although the drug easily crosses the blood brain barrier, IC_{50} levels are not attained in the cerebral cortex with doses of 5 or 10 mg/day, but remain in the range of 20%–34% inhibition,[75–77] findings which gave rise to the development of high-dose tablet (23 mg/day).[78] Rivastigmine is a so-called pseudo-irreversible inhibitor of both AChE and butyrylcholinesterase (BuChE), an enzyme of lower substrate specificity.[39,74] The clinical importance of BuChE inhibition is marginal. Rivastigmine is cleaved, at a low rate, by AChE, which slowly reverses the inhibition. The property of dual inhibition of AChE and BuChE is shared by two ChEIs used in earlier studies, physostigmine[79] and tacrine.[73] Tacrine was withdrawn mainly because of CYP-dependent hepatotoxicity[80–82] and poor efficacy.[83] Velnacrine, a tacrine derivative, exhibited a similar toxicity profile and was poorly effective.[84] Galantamine is a

competitive, reversible inhibitor of AChE, which binds to the anionic site of the active center.[85] Its affinity to BuChE is two orders of magnitude lower[85] and, thus, clinically irrelevant.

The differences between ChEIs concerning AChE and BuChE extend to the expression levels of these enzymes after treatment. In the CSF of AD patients, donepezil and galantamine increased AChE protein levels by 215 and 51%, respectively, and BuChE rather moderately, whereas rivastigmine decreased AChE and BuChE proteins by about 9 and 22%, respectively.[86,87] Whether such differences are relevant to a higher efficacy of rivastigmine in patients carrying the AChE A/A genotype[88] remains to be clarified.

ChEIs may possess additional properties that support cholinergic signaling. In preclinical studies, donepezil, rivastigmine and galantamine were shown to enhance the expression of the particularly relevant nicotinic receptor α7nAChR, and also non-α7nAChR receptors, in a region-specific manner.[89–91] However, α7nAChR is also upregulated in AD[92,93] and directly stimulated by $A\beta_{1–42}$ peptide.[94]

Various interactions of ChEIs with other neurotransmitter systems have been described or assumed, including serotonin and dopamine, but the clinical relevance has remained questionable.[95] The situation may be different in the case of α7nAChR and glutamate signaling, since nicotine[96] as well as donepezil and galantamine[91,97] were shown to protect against glutamate excitotoxicity via α7nAChR-dependent signaling, effects which are of interest with regard to the use of memantine, alone or in combination with ChEIs.

Several earlier reports that indicated inhibition of amyloid formation by nicotine have been mostly attributed to its direct binding to $A\beta_{1–42}$ peptide, but an involvement of α7nAChR signaling has been also discussed.[98] However, convincing data for clinical efficacy of ChEIs in substantially reducing amyloid deposits are not available.

It should be briefly mentioned that several other ChEIs have been recently developed. Some of them are derived from a natural plant constituent, cardenol.[99] Various others represent derivatives of tacrine,[100–103] despite the known hepatotoxicity of the parent compound. In two series, toxicity was reduced by using 7-methoxytacrine as a core compound.[100,101] The suitability of these drugs will largely depend on the outcome of safety studies.

N-methyl-D-aspartate receptor antagonists

Several NMDAR antagonists of weak to moderate affinity have been tested to counteract the increased glutamate release and NMDAR-dependent excitotoxicity observed in AD. One of them, dimebon (= latrepirdine), proved to be too weak, in therapeutic doses, and some clinical effects were later ascribed to inhibitions of histamine H_1 and serotonin $5\text{-}HT_6$ receptors.[104]

The adamantane analog, memantine, is actually the only approved drug of this category. The compound is an uncompetitive open-channel blocker of moderate affinity to the NMDAR (IC_{50} about 1 μM at −70 mV).[14,56] The additional property as a $5\text{-}HT_3$ antagonist is presumably not of therapeutic relevance.[105] Memantine does not compete with agonists, but rather enters the interior of the channel, where it prevents Na^+ and Ca^{2+} influx, similar to Mg^{2+} bound in the polarized state. The tolerability of memantine seems to be partially due to its moderate affinity which allows rapid blocking/unblocking kinetics and pronounced voltage-dependence.[56] Long-lasting inhibitions would be unfavorable under conditions of rapidly changing excitation. Other open-channel blockers such as (+)MK-801 and phencyclidine leave the channel too slowly after depolarization for being clinically suitable.[56] However, under excitotoxic conditions, in which depolarization is steadily sustained via AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-propionate) receptors, the partial NMDAR blockade by memantine is functionally effective to prevent an excessive Ca^{2+} influx.[14] Therefore, the fatal consequences of Ca^{2+} overload are avoided such as activation of Ca^{2+}-dependent enzymes, eg, neuronal NO synthase, and the reductions of mitochondrial electron flux and membrane potential.

Memantine is slowly but almost completely absorbed (t_{max} = 5–6 h) and has no substantial hepatic metabolism. It is slowly excreted. In patients without renal impairment, $T_{1/2}$ is in the range of 60–80 h.[14,106] At a therapeutic dose of 20 mg/d, the steady-state plasma concentration of about 90 μg/L is almost

attained after 10 d, with a minor increase thereafter. Similar values are obtained with 10 mg twice/d.[106]

AMPAR potentiators

Although glutamatergic overstimulation is a feature of AD, the observations that AMPA receptor (AMPAR) expression can decline during aging and is decreased in transgenic AD mice has prompted investigators to develop AMPAR potentiators for purposes of cognitive enhancement. CX717 (Ampakine®) has been tested preclinically and, clinically, in some non-AD trials, as summarized elsewhere.[107] The allosteric AMPAR activator S 18986 does exhibit properties of a cognitive enhancer in various animal models.[107] With regard to the undesired permanent glutamatergic stimulation in AD, one may be sceptic concerning its applicability in this disease.

Metal chelators and ionophores

An entirely different approach aims to intervene at the level of Aβ-related metal toxicity. Since attempts of reducing $A\beta_{1-42}$ formation by modulators of γ-secretase activity, such as tarenflurbil, were clinically unsuccessful in terms of cognition and daily life,[108] the focus of interest moved from Aβ peptide levels to the mechanisms of toxicity. Aβ is known to bind transition metal ions at histidines-6, -13, and -14 and alanine-2.[109,110] Two ions are of particular relevance in AD, namely, Cu^{2+} and Zn^{2+}. Zn^{2+}, which is loaded to synaptic vesicles by the zinc transporter ZnT_3, enters the synaptic cleft presynaptically by neuronal exocytosis,[111] whereas Cu^{2+} is released from the postsynapse by Menkes ATPase.[112] These normal processes are usually compensated by reuptake. In AD, however, binding of these metals to Aβ has several toxicological consequences. Aβ-metal complexes favor the formation of toxic soluble oligomers, which, among other effects, hyperactivate the NMDAR.[113] Moreover, the Aβ-copper complex can undergo redox cycling, which results in hydroxyl radical formation by a Fenton-like reaction.[114] Copper-dependent oxidation seems to also favor Aβ oligomerization by dityrosine crosslinks.[115] Binding of Cu^{2+} to alanine-2 carbonyl promotes amide hydrolysis at this peptide bond and leads to the truncated $A\beta_{3-42}$,[110] which is found in oligomers and amyloid plaques and which has been related to the severity of the AD phenotype.[116]

While considerable quantities of Cu^{2+} and Zn^{2+} are by time sequestered in amyloid plaques, intracellular stores of especially Cu^{2+} become gradually depleted. Intracellular Cu^{2+} deficiency has been discussed as a cause of further Aβ formation, which would lead to a vicious cycle.[117–119]

With regard to these mechanisms, a removal of Cu^{2+} and Zn^{2+} from the synaptic cleft by chelators that form stable complexes would be counterproductive, since this would aggravate intracellular copper deficiency. However, chelators that are capable of binding the metal ions and mediate, as ionophores, their re-entry into the cytosol and allow dissociation from the chelator, may be beneficial. Several compounds have been developed that fulfil these requirements.[113,119,120] One possibility is that of using a chelator whose complex stability depends on the redox state of copper, such as glyoxal-*bis* (N^4-methyl-3-thiosemicarbazonate).[113] In the extracellular space, it forms a stable Cu^{2+}-complex, but, in the cytosol, it becomes destabilized by reduction and releases Cu^{+}. Other examples are found among derivatives of 8-hydroxyquinoline.[113,119,120] The first-tested drug, clioquinol, is not recommendable because its Zn^{2+} complex is a potent mitochondrial toxin.[121] Actually, the best choice seems to be PBT2, a compound that is sufficiently amphiphilic to cross membranes as an ionophore and has only moderate affinities to Cu^{2+} and Zn^{2+} allowing a release of the ions to the cytosol.[113,119,120] Mode of action and efficacy have been confirmed in preclinical studies. In transgenic mice, several beneficial effects of this drug have been described: reduction of interstitial soluble Aβ; improvement of cognitive performance;[119] promotion of amyloid degradation;[122] stimulation of neurite outgrow; increases in dendritic spine density; higher levels of several regulatory proteins, such as CaM kinase II, BDNF (brain derived neurotrophic factor) and NMDAR subtypes;[123] and, finally, inhibition of glycogen synthase kinase 3 (GSK3) by phosphorylation,[122] ie, of an enzyme implicated in Aβ formation.

Multifunctional drugs

Several multifunctional drugs have been synthesized, which combine, in one molecule, properties of ligands to different binding sites. Some of the compounds were designed to bind to BuChE and/or to

allosteric and catalytic sites of AChE.[124–126] Several series of molecules were composed of tacrine or 6-chlorotacrine residues with donepezil, fragments of pyrano[3,2-c]quinoline moieties or multiply substituted phenyl groups.[124,125] All of them were reported to reduce Aβ aggregation in vitro.[124–127] Some hydroxylated derivatives also displayed scavenging of peroxyl radicals.[127]

Other hybrid molecules aimed to combine ChEI with antioxidant properties, by attaching residues of ferulic acid[128] or melatonin[129–131] to a tacrine moiety. Neither the toxicologic profile of tacrine was sufficiently considered in the design of these compounds, nor a possible interference with the numerous other functions of melatonin. Moreover, the antioxidant actions of reasonably-dosed melatonin are not primarily based on direct radical scavenging.[132] Nevertheless, a tacrine-melatonin hybrid was reported to reduce Aβ-dependent cell death and memory deficits in a mouse model.[131]

Several hybrids synthesized by combining donepezil and tacrine fragments were reported to be potent ChEIs with additional antiamyloidogenic activity in vitro.[133] Similar properties were ascribed to another hybrid in which donepezil was linked to a phenyl-N-methylbenzamino residue.[134] Tacrine-dihydropyridine hybrids were designed to combine ACh elevations with inhibition of voltage-dependent L-type calcium channels.[135,136] Using β-carbolines as a hybrid component, another approach was chosen to combine AChE/BChE inhibition with suppression of excitotoxicity via blockade of the NMDAR.[137]

Hybrids of rivastigmine and fluoxetine were synthesized to simultaneously inhibit AChE and serotonin reuptake.[138] Other hybrids combined rivastigmine with the monoamine oxidase (MAO) B inhibitor, rasagiline, or, to reduce iron-dependent oxidotoxicity, with an iron chelator.[139,140] Metal chelators were also attached to rasagiline, donepezil,[140] and *bis*-(7)-tacrine residues.[141] However, the tacrine dimer has, like the monomer, poor oral bioavailability.[142] A peculiarity of these donepezil, rasagiline and some rivastigmine hybrids is the liberation of the chelators upon cleavage by AChE.[140] The possible problems arising from the use of metal chelators has been discussed above. The tacrine moiety has also been combined with 8-hydroxyquinoline analogs, including PBT2.[143] Actions as ionophores remain to be directly shown. Additionally, they were reported to display antioxidant properties superior to Trolox.[143]

Another category of multifunctional drugs has been developed on the basis of a quinone/polyamine skeleton.[144–149] In the lead compound, memoquin, two polyamines attached to benzoquinone carry terminal methoxybenzene residues. Several of these compounds were shown to inhibit AChE, BuChE and Aβ aggregation. To enhance the antioxidant properties, memoquin/α-lipoic acid hybrids were designed.[148] In several recently developed molecules, polyamines have been combined with other aromates or heterocycles.[149]

The metabolism of these multifunctional drugs is almost unknown. A more complicated molecule bears more possibilities of metabolism and also of side effects. Safety studies will be required on a particularly broad scale.

Clinical Studies

The clinical outcome of ChEI[18–51] and memantine[11,14,52–65] treatment has been reviewed and meta-analyzed repeatedly, with extensive and detailed considerations in papers until 2009. More specialized reviews have been published until recently. Studies not incorporated into these summaries mainly concern ethnic populations, identification of non-responders, dosage, daily living, alternate routes of administration and combinations of ChEIs and memantine.

Three studies on donepezil in rather low numbers of Japanese patients were designed to discriminate between responders and non-responders on the basis of cognitive parameters,[150,151] donepezil positron emission tomography (PET),[151] or presence of the apolipoprotein E ε4 (ApoEε4) genotype.[152] Conclusions from these studies were not entirely consistent. While the first trial[150] identified non-responders especially among young patients with early disease onset, and the PET study indicated higher efficacy in patients with high ACh levels and high baseline attention,[151] the third one concluded that the drug is particularly effective in advanced AD.[152] A small, three-year study on donepezil treatment in Japanese patients with or without ApoE ε4 shall be briefly mentioned, although it started with Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale/Cognitive Subscale Japanese version (ADAS-Jcog) scores of about 24 and about 14, respectively.[153] Apart

from weak statistical tendencies for more pronounced MMSE declines and ADAS-Jcog increases in ApoEε4 patients, donepezil seems to have been more efficient in non-ApoEε4 patients. An open-label study on donepezil in 106 Hispanic patients with mild-to-moderate AD is of particular interest since this population has a higher incidence and earlier onset of AD.[154] A 6-month donepezil trial on behavioral symptoms in Spanish patients with mild to moderately severe AD indicated improvements in MMSE and especially Neuropsychiatric Inventory (NPI) scores.[155] A safety study of galantamine conducted in Thai patients included a dose-escalation phase.[156]

Effects of donepezil in mild to moderate AD (MMSE 26-10 at baseline) recently focussed on apathy in a meta-analysis of two earlier 6-month trials.[157] Studies on severe AD were conducted using either galantamine[158] or high doses (20, in a pilot study,[159] or 23 instead of 10 mg) of donepezil, aiming to overcome the poorer efficacy in advanced AD by higher levels of the drug.[78,160] Effects of dosage were investigated in a 24-week, randomized, double-blind multicenter, multinational study at 219 sites.[78] Other data from this study were analyzed with regard to language dysfunction[160] and to efficacy in more severe cases.[161] With regard to severity, a retrospective study analysis compared non-hallucinators with hallucinators, which mostly have stronger cortical cholinergic deficits and show a greater decline on placebo. Rivastigmine was more effective in the hallucinator group.[162]

Several trials have been conducted on combinations of ChEIs with other drugs. In depressed AD patients, combined treatment of ChEIs (67% of patients donepezil, 20% rivastigmine, 13% galantamine) with serotonin reuptake inhibitors (citalopram, escitalopram, sertraline, fluoxetine, paroxetine) was compared with ChEI treatment only in depressed and non-depressed persons, over 9 months with individually escalating ChEI doses.[163] Findings indicate advantages for cognitive measures by the combined treatment, although some reservations have to made with regard to the heterogeneity of medication. A combination of donepezil with a mixture of antioxidants tested in a small number of patients claimed cognitive improvements relative to donepezil alone.[164] However, the complex pharmacology of the mixture may justify some reservation. An exploratory double-blind, placebo-controlled study compared the efficacy of donepezil and the 5-HT_6 antagonist SB-742457.[165] Although some improvements were described for the serotonergic antagonist, donepezil seemed to be superior. A combined treatment might be worth an investigation.

Memantine, which has been approved for treatment of moderate to severe AD, has been investigated in two 6-month postmarketing surveillance studies.[59,65] A proportion of about 27% responders showed no deterioration at time of assessment.[59] Significant behavioral improvements were reported for the memantine group.[65] Decreased agitated and aggressive behavior was also observed in a small open-label study on long-term care residents.[166] A recent development, the combination of memantine and ChEIs, has been addressed in a safety study on rivastigmine capsules plus memantine,[167] an evaluation of safety, cognitive and global functions with rivastigmine transdermal patches and oral memantine,[168] a published study design for donepezil plus memantine,[169] and a long-term study on non-specified ChEIs plus memantine.[170] After a follow-up of at least one year, cognitive measures were approximately the same in patients with ChEI monotherapy and those treated with the combination.[170] Psychiatric symptoms were, on the average, lower in the combination cohort, but statistically not significant. Comparisons with memantine monotherapy were not provided.[170]

In conceptual terms, the majority of new studies mentioned do not substantially deviate from earlier ones and the progress obtained thereof is limited, relative to previous knowledge. A few minor advances, in addition to earlier data, may have been made concerning the subpopulations of patients that do not or poorly respond to ChEI treatment, such as carriers of the ApoEε4 genotype. Another tendency concerns the study of combinations of ChEIs with either antidepressants or memantine. In the first case, tests of this type can be meaningful because of symptoms of depression in many AD patients. However, future trials should focus more on homogeneous cohorts, in which a single antidepressant is studied in a higher number of patients. The combination with memantine, performed in the hope of improvements in more severe cases of AD, still requires convincing support of superiority over monotherapies. For the moment, it seems justified to conduct more studies using higher ChEI doses in severe AD, as already done with

donepezil,[78,160,161] even though the improvements may remain moderate. The newly developed rivastigmine transdermal patches may be regarded as an innovation, which concerns the ease of administration, the longer-lasting bioavailability because of extented absorption, and reduction of emetic events. Safety, skin tolerability and efficacy of this method have been compared, in several studies of different design, with capsules of the same drug and after a switch from donepezil.[40,45,171–180]

Published data on the Cu/Zn ionophore PBT2 are to date only available for two analyses of a phase II trial in which doses of 50 and 250 mg had been tested.[181,182]

Safety

Adverse effects/events (AEs) of ChEIs are mostly related to ACh elevations. They mainly concern the gastrointestinal tract, less frequently heart and CNS. Safety studies and reviews consistently report that donepezil, rivastigmine and galantamine are usually well tolerated and that most AEs are mild. Such statements somewhat contrast with the frequencies of gastrointestinal AEs, at standard therapeutic doses: nausea (11%, 44%, 24%), vomiting (7%, 30%, 14%), and diarrhea (12%, 13%, 8%) for donepezil, rivastigmine (capsules) and galantamine, respectively, according to a meta-analysis of 26 trials.[183] Other more frequent AEs are weight loss (7%, 11%, 10%) dizziness (8%, 22%, 10%)[183] and, with lower incidence, headache, abdominal pain, and muscle cramps.[18,20,23,32] Insomnia and vivid dreams may be sometimes associated with donepezil, and weakness or fatigue with rivastigmine and galantamine.[184,185] A higher donepezil dose of 23 mg/d, instead of 5 or 10 mg/d, developed for the treatment of moderate to severe AD, was associated with increased AE frequencies, which remained, however, in the lower percent range.[78]

Replacement of galantamine immediate release (12 mg twice per day) by an extended release formulation (24 mg/day; 25% immediate release; 75% controlled release) has been reported to not substantially augment AEs.[49] In a preclinical study, AEs have been strongly reduced by using the galantamine prodrug, Memogain® (Gln-1062),[186] which may be a future option. Another possibility may be intranasal administration of galantamine (as lactate instead of hydrobromide),[187,188] which avoids first-pass metabolism and high gastrointestinal concentrations. In an animal model, this led to strongly reduced AEs,[187] but clinical confirmation and dose adjustment would be required.

In order to circumvent the short action of oral rivastigmine and to avoid high gastrointestinal levels, rivastigmine transdermal patches have been developed. Compared to capsules, emetic AEs were strongly reduced.[39,40,42–45,71,172,173,175,177,189] Nausea and vomiting occur only in the 4% range. Dermatological AEs, which are generally possible with patches, have been observed but are infrequent.[38,42] Case reports have described allergic contact dermatitis[190] and a delayed hypersensitivity reaction.[191] A case of hepatitis with cholestasis reported in conjunction with rivastigmine patches[192] should be seen as an exception. Rivastigmine's negligible liver metabolism would not explain hepatotoxicity. A case of hepatotoxicity was reported for a patient treated with the long-acting, hepatically metabolized donepezil.[193]

Nevertheless, rarely occurring, but severe AEs deserve particular attention, eg, concerning exceptionally strong vagotonic effects on cardiac function. After several case reports on bradycardia, syncopes and atrioventricular block in patients treated with ChEIs, a thorough study on a very large cohort has determined AE frequency, multivariate-adjusted hazard ratio (HR) and contributing risk factors.[194] A moderately increased HR of bradycardia is demonstrable with all approved ChEIs, with greatest risk for higher doses of donepezil, but the overall treatment-related incidence remained below 0.02%. Increases of total or cardiovascular mortality due to donepezil were not evident.[195] Over 120 cases of overdoses reported for rivastigmine transdermal patches, with sometimes dramatic AEs, have been caused by inappropriate use, especially failure to remove old patches or simultaneous application of several patches.[196]

Pleurothotonus (Pisa syndrome), another rare AE with considerable inconvenience to the patient, has been observed with all three approved ChEIs. The dystonia is resolved after discontinuation.[197]

AEs due to drug interactions are highly divergent among the ChEIs in use, because of considerable differences in hepatic metabolism. While rivastigmine is not a CYP substrate, the pharmacokinetics of donepezil and galantamine is strongly affected by CYP3A4

and CYP2D6 inhibitors, such as ketoconazole and paroxetine.[19,48] Another type of drug interaction is related to anticholinergic effects of some antihistamines and tricyclic antidepressants, which lead, however, only to reductions in ChEI efficacy.[198]

In patients treated with the NMDAR inhibitor, memantine, AEs are almost indistinguishable from those with placebo.[11,14,198] Constipation, headache, hypertension and somnolence were reported to occur in the low percent range.[185] Hallucinations and aggressive reactions were observed in an open-label study.[199] A warning concerning heart failure due to memantine treatment[200] concerns rare exceptions, but should be taken as a caveat in patients with cardiovascular diseases. Memantine, which is devoid of substantial hepatic metabolism,[14] does not show drug interactions based on CYP isoforms. With regard to multiple interconnections between central nervous neurotransmission systems, interactions with neuropharmacological drugs are not unlikely. Hallucinations induced by combination of memantine with riluzole have been observed.[201]

The ionophore PBT2 was reported to be safe and devoid of serious AEs, in a Phase IIa trial,[181] but final conclusions should not be drawn without confirmation in more extended studies. Since the application will require long-term administration, the tolerability of the high dose of 250 mg/day may become a crucial issue.

Efficacy

Most of the studies on ChEIs have been conducted in patients with mild to moderate AD. However, these findings cannot be neglected here, because of a considerable overlap of MMSE and ADAS scores with cohorts of moderate to severe AD. Most of the trials, meta-analyses and reviews accordantly state that the efficacy of the three approved ChEIs is only moderate and temporally limited.[9,18–20,22–31,37,38,41,46,47,49,50,95,150–154,171,179,183,202–206] This judgment has not substantially changed over the years. Occasionally, the usefulness of ChEIs has been questioned, either under aspects of cost-effectiveness or with regard to possible sponsors' influences on the publication of vendor-supported trials.[207] However, the very large body of evidence for an, albeit modest, efficacy is clearly in favor of the usefulness of ChEIs. This is not contradictory to a percentage of non-responders related to disease stage or genetic disposition,[208,209] or to trials without demonstrable efficacy, because of unfavorable cohort size, heterogeneity or study design.[45,150–152]

The multiply reviewed beneficial effects of ChEIs concern cognitive measures such as MMSE, ADAS-cog, and Severe Impairment Battery (SIB); global assessments such as Clinician's Interview-based Impression of Change (CIBIC; with variant CIBIC+ including caregivers' input), Gottfries, Brane and Steel scale (GBS), and Global Deterioration Scale (GDS); measures of daily living activities such as Progressive Deterioration Scale (PDS), Disability Assessment of Dementia (DAD) and the AD Cooperative Study Activity of Daily Living scale (ADCS); for assessment of behavioral disturbances, the Neuropsychiatric Instrument (NPI), all based on several subscales. Depending on studies, improvements are not always observed in every domain or subscale. With regard to efficacy, donepezil, rivastigmine and galantamine show a considerable overlap in the various domains, so that fundamental differences cannot be deduced. Although some evaluations have indicated minor deviations in efficacy,[18,20,183,202] eg, concerning the starting dose,[18] they do not justify a preference for one of these drugs. Rivastigmine capsules and transdermal patches were found to be approximately equally effective.[44,176,179,180] Small clinical improvements relative to baseline are mostly seen during the first 6 months,[25,74,171] but longer-lasting beneficial effects are observed relative to placebo. In moderate AD, the decline in especially cognitive measures can be significantly slowed over a year or even longer,[74,171,205,210,211] but this should not be misinterpreted in terms of halting the disease. Differences in the various domains of assessment are frequent during prolonged treatment. In a number of patients with active treatment, cognitive measures more slowly decline than in the placebo group, whereas benefits in psychiatric, global and daily living measures may disappear, however, with considerable interindividual variation.

In many studies and meta-analyses on behavioral and psychological symptoms, no data are provided for NPI or CGIC subscales. Therefore, symptoms as different as agitation/aggression, anxiety, apathy and hallucinations are merged. Because of the particular importance for the patient's life, it should be emphasized that relatively marked improvements are frequently observed in the reduction of apathy with

donepezil,[157] galantamine,[51] and rivastigmine.[212–215] This should be expected with drugs enhancing the availability of an important activating neurotransmitter with multiple influences on other activating systems. Although apathy is usually regarded as a "noncog" symptom, its improvement may be a cofactor in cognitive ameliorations, and facilitation of daily living, too. Merging apathy and other subscales, especially that of agitation/aggression, can obscure the final outcome. Improvements in the agitation/aggression domain by a ChEI, frequently mentioned, would be less plausible from a mechanistic point of view and have been questioned.[216]

The usefulness of ChEIs in severe AD has been differently judged. Earlier studies on donepezil in moderate to severe AD revealed benefits in MMSE and SIB scores. Post hoc analyses on subcohorts with more advanced disease also indicated positive effects on cognitive measures (MMSE and ADAS-cog) for rivastigmine and galantamine.[210,217] For donepezil, findings were confirmed in a recent pooled data analysis on patients with different baseline MMSE scores, including a group starting with 1–5 points.[36] In the advanced AD stages, the higher donepezil dose of 23 mg/d has been tested and found to be superior to the standard dose of 10 mg/d in these patients.[78,161] In addition to measures of cognition and global functioning, greater benefits of the high dose were observed in attenuating language dysfunction.[160] Higher doses have also been tested with rivastigmine transdermal patches (17.4 instead of 9.5 mg/d).[180] Although this caused improvements of MMSE and ADCS-ADL scores in moderate and moderately severe AD, changes in severe AD revealed only non-significant trends. Effects on CGIC were statistically demonstrable in severe AD, but remained very modest in their extent.[180] An advantage of the higher dose was not convincingly demonstrated. In patients with MMSE scores of 5–12 points, galantamine was found to slightly improve SIB domains of memory, praxis and visuospatial ability, in contrast to worsening in the placebo group.[158]

According to the approval, most studies on memantine have been conducted in patients with moderate to severe AD. This drug, which is not primarily acting on ACh levels, but rather antagonizes overexcitation and inflammation-related excitotoxicity, should differ from ChEIs in influencing the various measures of cognition, daily functioning and behavior. Statistically significant improvements have been reported for most relevant measures, such as SIB, MMSE, ADAS-cog, CIBIC+, ADL, FAST (Functional Assessment Staging Tool), GDS, NPI, or subscales thereof.[11,14,52–54,57,59,63–65,166,199,217] However, a closer look reveals that these benefits are often only demonstrable for some of these parameters in the single trial. Moreover, statistically significant improvements have sometimes been considered clinically marginal, with a same rating for ChEIs.[218–220] As a general tendency, positive effects seem to be rather modest in cognitive scores. Typically, the benefits consist in a delay of worsening for about three months. Some hopes of a better outcome have been expressed for the use of a higher dose (28 mg/d) of an extended-release formulation, instead of 10 mg immediate release twice a day.[62] With regard to the slow, but complete resorption and long-lasting persistence of memantine in the plasma, this idea may be critically seen. A possibly important observation, with considerable implications for the caregivers' burden, concerns significant reductions in agitation and aggression.[57,64,166] This may not be surprising for a drug that reduces glutamate-dependent neuronal excitation. Thus, the question arises to what extent these behavioral/psychiatric symptoms are explained by mild sedation or by improvements in neurological functions. The latter possibility may be favored by other findings on reductions of language impairment, using the SIB-language (SIB-L) scale.[60]

In the last years, combinations of ChEIs, mostly donepezil, with memantine have been or are being explored.[37,61,169,170,211,221–227] This might be of particular interest for advanced AD stages, also with regard to the approval of donepezil and memantine in severe AD. Despite reports on further improvements in subsets of responders, the evidence for a general superiority of the combination over the respective monotherapies is still weak and requires further investigation.

Among the numerous investigational drugs mentioned, clinical data are only available for the ionophore PBT2. The phase II trial was conducted for only 12 weeks, on a relatively small number of patients with mild AD, who were also treated with ChEIs. Cognitive improvements were only demonstrated in several scores of the Neuropsychological Test Battery (NTB), but remained non-significant in MMSE and ADAS-cog scales.[181,182] This should not

yet justify a conclusion on poor efficacy. This drug, which acts on Aβ levels, Aβ-related metal toxicity, release from amyloid and distribution of transition metals, may require much more time than 12 weeks for profound improvements. It seems also important to not reduce the discussion on PBT2 to antiamyloid activity and, thus, to confound this with negative findings on drugs like tramiprostrate and tarenflurbil, which do not antagonize Cu and Zn toxicity. Whether PBT2 will be suitable for treating moderate to severe AD remains to be studied.

In summary, most of the recent findings in moderate to severe AD do not deviate in their essence from that what has been known before. ChEIs and also memantine are moderately and transiently effective in responders to active treatment. In the course of disease progression, the therapeutic success decreases. Higher doses of donepezil (eg, 23 mg/d) and, perhaps, of the other ChEIs can partially overcome this difficulty. However, elevated doses of memantine extended-release appear to be unnecessary under aspects of pharmacokinetics and bioavailability. The positive effects of memantine on non-cognitive measures such as reduction of aggression and agitation, deserve particular consideration. Whether or not combinations of donepezil and memantine lead to substantial improvements in late AD remains an open question.

Patient Preference

Preferences of demented patients may be, in part, deduced from frequency and reason of discontinuations because of adverse events. In larger trials on ChEIs, dropouts are mostly in the range of 15%–18% for donepezil and galantamine standard doses, and of 19%–29% for rivastigmine capsules, compared to <10% in the placebo groups, however, with considerable inter-study variation.[23,32,40,46,78] Among quantitatively relevant AEs, emetic effects prevail and represent a major cause of discomfort. Increased doses of the three ChEIs are associated with higher frequencies of withdrawal.[20,32,46,78] Gastrointestinal AEs are markedly reduced in rivastigmine transdermal patches.[40,43,172] Nevertheless, the frequency of treatment-associated discontinuation is still in the 15% range, due to other causes. As long as no skin irritations or problems because of continually elevated plasma levels occur, patients may prefer rivastigmine patches. The patches may also be of advantage in patients who have difficulties in swallowing.

With memantine, AEs and discontinuations are almost indistinguishable from the placebo groups.[11,14,185,199] Therefore, patients might have a preference for this drug. However, usefulness and responsiveness have to be decided by the physician. The reductions of aggression and agitation by memantine are certainly of advantage for the caregivers, and a more balanced mood may be positively perceived by patients as well.

Place in Therapy

Donepezil, rivastigmine, galantamine and memantine are to date the only drugs approved for the treatment of moderate AD, donepezil and memantine those for severe AD. As long as no causal therapy of the disease is available, these four drugs offer the only accepted methods of treatment, despite their limited efficacy. In responders, all of them are capable of improving cognitive and other measures for several months and of slowing the decline of the respective functions over extended periods. Attempts of identifying, prior to therapy, patients that will presumably not respond seems useful, but this may not be possible with high certainty. It is even more important to identify, before ChEI treatment, patients with high risks for AEs, especially those with cardiovascular diseases. Comorbidities and concomitant medications possibly causing drug interactions deserve particular attention before prescribing ChEIs.

The drugs differ less with regard to cognitive enhancement, but in behavioral functions and AEs. ChEIs have advantages in counteracting apathy, whereas memantine seems to be favorable in reducing aggressive behavior and agitation. AEs are more pronounced with ChEIs than memantine and especially concern emetic responses. In the case of rivastigmine, the undesired gastrointestinal effects are largely reduced by transdermal patches, which is an advantage over capsules and other ChEIs. If Memogain® will be approved in the future, this prodrug of galantamine may replace the active drug. Other methods of ChEI administration, such as the use of intranasal sprays, may also reduce AEs.

Higher doses for the treatment of severe AD seem to be favorable, in the case of donepezil, with regard

to cognitive and global functions, whereas this is less evident for memantine. The use of elevated doses may be limited by increased frequencies of AEs. Especially in severe AD, the combination of donepezil and memantine has been suggested. Whether this will be a future gold standard,[227] remains uncertain, as long as the combination has not convincingly shown substantial superiority over monotherapies.

Treatments with ChEIs and/or memantine should not only be regarded under the aspects of modest efficacy or cost-effectiveness. Even temporally limited improvements and slowed declines in functions of cognitive, daily living and global measures represent a gain for both patients and caregivers. Reductions in apathy can be valuable for interacting with the patient and his/her—albeit limited—participation in daily life, and those in agitation and aggression represent a considerable relief to caregivers.

Conclusions

Although donepezil, rivastigmine and galantamine differ considerably in their pharmacokinetics, bioavailability, metabolism and inhibitory mechanisms, their clinical efficacy, safety and tolerability profiles are similar. The additional property of rivastigmine of inhibiting both AChE and BuChE does not seem to be of clinical relevance. Severe AEs of ChEIs are rare, but others frequent or very frequent. Attempts have been undertaken to reduce especially emetic AEs. For regular clinical use, this is to date only possible with rivastigmine transdermal patches. The efficacy in improving cognitive, behavioral, functional and global symptoms and in delaying a further decline is moderate with all three ChEIs. It is not possible to halt the disease by these treatments.

Memantine, an uncompetitive open-channel blocker of the NMDAR, with moderate affinity and rapid blocking/unblocking kinetics, reduces neuronal overexcitation and neuroinflammatory excitotoxicity. AE frequencies are relatively low. The clinical outcome is, however, similarly moderate as with ChEIs. A difference to those drugs exists in a more effective reduction of agitation and aggression. Efficacies of monotherapies and combinations of ChEIs and memantine differ only marginally.

Many attempts have been undertaken to develop alternate strategies of treatment. Preclinical studies and a phase IIa trial on the Cu/Zn ionophore PBT2 are encouraging, but its suitability will depend on efficacy and non-toxicity during prolonged treatment. Several investigational drugs, such as the AMPAR potentiators CX717 and S 18986 as well as numerous multifunctional hybrid molecules, await thorough preclinical or clinical investigation. However, these pleiotropically acting drugs are still designed for symptomatic treatments. Whether they will be superior to currently approved drugs remains to be shown. As long as the etiology of AD is not understood in its initial causes, it is impossible to develop, on a rational basis, drugs that definitely halt the disease.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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