Anti-dementia Medication

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List of Abbreviations

ADL	Activities of daily living
AEs	Adverse events
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive Subscale
ACh	Acetylcholine
AChEI	Acetylcholinesterase inhibitor
APOE	Apolipoprotein E
APOE-ε4	Apolipoprotein E epsilon 4
Aβ	Amyloid beta
BuChE	Butyrylcholinesterase
CYP	Cytochrome group of enzymes P450
DLB	Dementia with Lewy bodies
FDA	Food and Drug Administration

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K. S. Frederiksen, G. Waldemar (eds.), *Management of Patients with Dementia*,
https://doi.org/10.1007/978-3-030-77904-7_5

LBD	Lewy body dementia
MRI	Magnetic resonance imaging
MCI	Mild cognitive impairment
PDD	Parkinson disease dementia
REM	Rapid eye movement
DOMINO-AD	UK Donepezil and Memantine in moderate to severe AD
VaD	Vascular dementia

Introduction

The most common aetiology of dementia is a neurodegenerative process in the brain triggered by various proteinopathies and consequent differences in pathophysiological, clinical and biomarker phenotypes that are summarised under specific diagnoses (Chap. 2). The core trigger of neurodegeneration in the most common sporadic forms of primary degenerative dementias is still unknown (or under debate) and starts years before the clinical symptoms of the disease. As a result, there are currently no specific preventive strategies or disease-modifying therapeutics available. Clinical symptoms of dementia are due to a progressive loss of neuronal function that is mediated by signal substances or neurotransmitters in the brain cells' synapses. In the early 1990s this was one of the underlying ideas behind the first specific anti-dementia treatment for the most common form of dementia: Alzheimer's disease (AD). Today it continues to be the only evidence-based, first-line treatment approach. A limited and transient symptomatic effect of current medications without substantial and sustained long-term benefit is driving research efforts towards new treatment strategies in the hope of achieving disease-modifying effects. In this context drug targets are changing, and the amyloid cascade hypothesis occupies a key role in the development of new drugs. Accordingly, focus on target patient population further to the "left" on the clinical trajectory of disease evolution, i.e. towards early or prodromal stages of AD such as mild cognitive impairment (MCI), preferably well phenotyped with molecular and imaging AD biomarkers.

History of Pharmacological Treatment of Dementia

Current anti-dementia medications stem from the anticholinergic hypothesis of AD [1], which is based on converging evidence of reduced choline uptake and acetylcholine (ACh) release, degeneration of cholinergic cells in the nucleus

basalis of Meynert with consequent loss of neocortical cholinergic innervation [2, 3]. In parallel, experimental studies demonstrated the role of ACh in learning and memory [4].

In 1993 tacrine was the first centrally acting cholinesterase inhibitor approved for the treatment of AD. Though the initial reports on the efficacy of the drug were very good, it was quickly taken off the market due to its hepatotoxicity. Tacrine caused elevated hepatic enzymes and its metabolite was cytotoxic [5].

In 1996 donepezil was approved for the treatment of mild to moderate AD, supported by the outcomes of 19 randomised clinical trials (RCTs) (three in severe stages of the disease and 16 in the mild to moderate stage) designed to assess treatment efficacy on cognition, function and/or behaviour and neuropsychiatric symptoms [6, 7].

In 2006 the US Food and Drug Administration (FDA) approved donepezil for the treatment of severe AD just 1 month after data from a Swedish study on severe AD in nursing home settings were published [8, 9].

Rivastigmine entered market in 2000, supported by the outcomes of six RCTs showing its efficacy in terms of the three above-mentioned symptom domains in mild to moderate AD. One RCT was performed in severe stages of the disease [10]. Due to a higher frequency of adverse events (AE), in particular gastrointestinal (GI) ones, the rivastigmine transdermal patch with gradual release over 24 h was developed in 2007 [11, 12]. In 2013 the FDA expanded the approved indication for the rivastigmine patch (13.3 mg/24 h) to include the severe stages of AD.

Approved in 2001, galantamine is the most recent acetylcholinesterase inhibitor (AChEI) used in treating AD, also mild to moderate AD, its efficacy assessed in eight RCTs (one in severe stages of the disease and seven in mild to moderate stages) [10]. Due to faster elimination, a half-life extended-release oral product was developed to permit single instead of the original twice-daily intake.

In 2003 the FDA approved memantine for the treatment of patients with moderate to severe probable AD, its efficacy assessed in six clinical trials (three in moderate to severe AD and three in mild to moderate) [10].

In 2014 the FDA approved donepezil-memantine as an extended-release capsule for patients stabilised on daily dose of donepezil 10 mg and not currently on memantine. The recommended starting dose is 7 mg/10 mg, taken once a day in the evening, which should be increased in 7 mg increments until reaching the recommended maintenance dose of 28 mg/10 mg once daily [13]. This drug formulation is not approved in Europe (Table 5.1).

Table 5.1 Six-month randomised double-blind clinical trials of AChEI and memantine efficacy in AD patients (Data from Cochrane Database of Systematic Reviews)

Drug	Legislation (year)	Indication	6-month RCTs[a] number (year)	No. of patients	MMSE (range)	Efficacy			
						Cognition	Global change	Function	Behaviour
Donepezil	1996 (USA) 1997 (Europe)	Mild to moderate AD	6 (1998–2011)[a]	1893	17–22	+	+	+	-
	2005	Moderate to severe AD	8 (2001–2017)[b]	3522	1–14	+/–	+	+	-
23 mg ER tablet	2010 (USA)	Moderate to severe AD	Evaluated in 2 of 8 studies						
Rivastigmine	1998 (Europe)	Mild to moderate AD	7 (2000–2011)	4938	10–26	+	+	+	-
	2000 (USA)	Severe AD (capsules)	1 (2005)	218	5–12				
	2013	Severe AD 13.3 mg (transdermal patch)							
Galantamine	2000 (Europe)	Mild to moderate AD	5[c] (1997–2005)	3792	10–24	+	+	+	+/–
	2001 (USA)	Severe AD	1 (2009)	505	5–12	+	-	-	-
Memantine	2002 (Europe)	Moderate to severe AD	11 (2003–2011)	3732	3–14	+/–	+/–	+/–	+/–
	2003 (USA)	Mild to moderate	4 (2004–2011)	1672	10–23	+/–	+/–	+/–	+/–

In the Efficacy column, treatment-related change in domain-specific outcomes across the RCTs has the following annotations: + positive change; - absence of change or negative trends; +/- no conclusive evidence across the studies

AChEI acetylcholinesterase inhibitor, *AD* Alzheimer's disease, *ER* extended release, *MMSE* mini-mental state examination, *RCT* randomised controlled trial

[a]Only late-stage 6-month RCTs using minimal effective dose of donepezil 5 mg reporting sufficient data and at least two out of four domains included as primary outcomes (according to Birk 2018).

[b]Tariot et al. study [7] was included for moderate to severe AD since patients were nursing home residents with a mean MMSE of 14.4, broad score range of 5–26

[c]Five- and seven-month RCTs also included

Pharmacodynamics and Pharmacokinetics: Relevant Information for Clinicians

The pharmacodynamics of drugs refers to the underlying mechanism of its biological effect and biochemical and molecular interactions. An important aspect of pharmacodynamics involves identifying which intrinsic and extrinsic variables affect the relationship between the concentration and effect of the drug [14].

The pharmacokinetic characteristics of drugs, such as release, absorption, distribution, bioavailability, metabolism and excretion are crucial for determining a daily effective dose, minimum and maximum dose, dosage regimen and form of administration [14] (Table 5.2).

Acetylcholinesterase Inhibitors

The three AChEIs currently in use decrease the breakdown of acetylcholine (ACh) in the synaptic cleft, potentiating the effect in the synapse of ACh by inhibiting the enzyme cholinesterase, which has two major forms: AChE and butyrylcholinesterase (BuChE). The former is highly selective to ACh and hydrolysing it to acetate and choline terminates its action in the synapse. Contrary to AChE, BuChE also metabolises other endogenous and exogenously applied molecules, such as certain neuropeptides, and centrally active substances such as organophosphates.

Although the main mode of action of donepezil, rivastigmine and galantamine is similar, their pharmacological properties differ (Table 5.1). Non-competitive inhibition of donepezil and rivastigmine means that they bind and inhibit AChE irrespective of whether it has already been bound to its substrate ACh, in contrast to galantamine, which competes with ACh for the binding site on AChE. The reversibility of enzyme inhibition is a major requirement for the therapeutic non-toxic effect of AChEI.

AChE exists in two isoforms in the nervous system, G1, which is selectively present in the cortex and hippocampus, while the G4 isoform is predominant in the motor endplate in the peripheral nervous system (Weinstock, 1999). The higher selectivity of rivastigmine to the G1 isoform explains the absence of peripheral cholinergic effects, such as muscle cramps and weakness, described as side effects of donepezil and galantamine. An additional advantage of rivastigmine compared to the other AChEIs is that AChE activity, particularly its G4 isoform, decreases during the disease course and G1 isoform is probably mainly responsible for hydrolysing ACh. Furthermore, rivastigmine is not specific for AChE over BuChE [15], the latter less affected by the disease or even increased [16]. However, rivastigmine has a noticeably short elimination half-life compared to donepezil and galantamine, which requires two oral daily doses to reach a steady-state concentration in the plasma. More than one daily dose of a drug compromises compliance with treatment in patients with dementia. Another disadvantage of rivastigmine is that plasma concentration of the drug increases more than proportionally when the dose increases. Nonlinear pharmacokinetics results in more side effects in comparison

Table 5.2 Pharmacodynamic and pharmacokinetic properties of acetylcholinesterase inhibitors

Properties	Donepezil	Galantamine	Rivastigmine	Memantine
Mode of action	Non-competitive, rapidly reversible inhibitor	Competitive, rapidly reversible + nAChR modulation	Non-competitive, slowly reversible	Non-competitive, low-affinity, NMDA receptor antagonist
AChE/BuChE selectivity	300	50	1	
Brain vs peripheral selectivity	Yes	No	Yes	
Formulation	Tablets (ER) (5, 10, 23 mg)	Tablets (ER) (8, 16, 24 mg) Oral solution (2 mg/ml)	Capsules (1.5, 3, 4.5, 6 mg) Oral solution (2 mg/ml) Transdermal patch (4.6, 9.5, 13.3 mg/24h)	Tablets (10, 20 mg)
Effective dose(s)	5–10, 23[a] mg (once daily)	16–24 mg (once daily)	6–12 mg (divided into two daily doses)	10–20 mg (once daily)
Absorption affected by food	No	Yes	Yes	No
Bioavailability (%)	100	100	35 (3mg), 70 (6mg)	100
Time to reach $C_{max,ss}$ (h) (t_{max})	6	4–5	1 (capsule), 8 (patch)	3–8
Elimination half-life (h) ($t_{½}$)	73	6–8	1.5–2 (capsule), 3.4 (patch)	60–70
Metabolism	Hepatic (CYP2D6, CYP3A4, UGT)	Hepatic (CYP2D6, CYP3A4, UGT)	Esterases in liver and intestine	Mainly unmetabolised
Renal excretion (%)	17	50	Metabolite	57–82 (pH dependent)
Kinetics	Linear	Linear	Nonlinear	Linear
Steady state (days)	14–21	6	1	11

nAChR nicotinic acetylcholine receptors, *NMDA N*-Methyl-D-aspartate, *AChE* acetylcholinesterase, *ER* extended release, $C_{max,ss}$ maximum steady-state plasma drug concentration during a dosage interval, *CYP* cytochrome P450, *UGT* uridine 5'-diphospho-glucuronosyltransferase
[a]Donepezil ER 23 mg only approved in USA

with donepezil and galantamine. The rivastigmine patch has considerably better tolerability since it gradually releases the drug over 24 h [17, 18].

A further distinctive pharmacokinetic characteristic of galantamine is its dual mode of potentiating cholinergic transmission by additional interaction with nicotinic receptors. This effect was expected to be extra beneficial since the severity of cognitive impairment in AD correlates with loss of nicotinic receptors [19].

An important aspect of pharmacokinetics is an effect of renal and hepatic metabolism on drug elimination, which differs among AChEI with consequent effect on drug interactions and frequency of adverse effects of treatment [20].

Donepezil is metabolised in the liver by the cytochrome group of enzymes P450 (CYP) (Table 5.1), and the primary route of elimination is renal. No dose adjustments are needed in subjects with moderate renal dysfunction. However, even in mild to moderate liver impairment, the recommended 5 mg dose should be maintained. There is only one active metabolite with low affinity and negligible effect on AChE inhibition and pharmacological effect of the drug. Drugs that are potent CYP inhibitors (ketoconazole, cimetidine) influence plasma concentrations of donepezil considerably.

Rivastigmine is mainly metabolised by cholinesterase-mediated hydrolysis in the liver and to negligible extent in the intestines, to inactive metabolites (Table 5.1). CYP enzymes are not significantly involved in the rivastigmine metabolism, making drug interactions unlikely. Renal excretion is also a primary route of elimination, with no need for dose reduction in mild to moderate renal impairment. Since dose titration to tolerability is the basis for individually determining the maximum treatment dose, even in moderate liver cirrhosis, there is no general recommendation about the maximum dose.

Up to 30% of galantamine is excreted unmetabolised in the urine, while the rest is metabolised through various pathways, e.g. as CYP enzymes and glucuronidation, which provides active metabolites, though in low concentrations, in the plasma and a doubtful contribution to the pharmacological effect of the drug. Use of galantamine in patients with moderate to severe hepatic dysfunction is not recommended due to an up to 60% reduction in metabolic clearance.

Memantine

Memantine is a non-competitive, low-affinity antagonist of the *N*-methyl-D-aspartate (NMDA) ionotropic channel receptor, which is a binding site for a major excitatory neurotransmitter glutamate. Pathologically increased NMDA receptor activity has been demonstrated in AD, as well as impairment of learning and memory, with their blockade [21]. Memantine's low-binding affinity restores homeostasis in the glutamatergic system without accumulation in ion channels or blocking of synaptic neurotransmission [22]. Memantine is believed to have both a symptomatic treatment effect and neuroprotective properties [23].

CYP enzymes do not contribute significantly to metabolism of memantine to its inactive metabolites; however, memantine seems to be both a potent and selective inhibitor of CYP2B6 enzyme in its therapeutic doses, which might have clinical relevance in terms of drug interactions [24]. Since memantine and its metabolites are excreted renally by tubular secretion, concomitant therapy with drugs with a similar route of elimination could lower clearance of memantine. However, the widely used oral antidiabetic metformin did not have pharmacokinetic interactions with memantine during a single-dose, 6-day treatment in healthy volunteers, despite the similar route of elimination [25]. In patients with severe renal impairment only half of a maximum daily dose is recommended, while in moderate renal

insufficiency tolerance during the titration phase with 10 mg is the guiding principle in determining the individual maximum dose.

Pharmacogenetics: Towards a Personalised Treatment

Genetic variations in drug metabolising enzymes as well as AChEs could contribute to the individual therapeutic failures and different side effects or AEs across the different compounds from the same class, Table 5.2. Different profiles of common genetic risk factors for AD, such as DNA apolipoprotein E epsilon 4 (APOE-e4) genotype, might also have impact on treatment response in AChEIs. A number of studies performed on genetic polymorphisms in cytochromes [20], in particular CYP2D6, for AChEI treatment identified several groups of metabolisers: 5–10% of poor metabolisers, 10–17% of intermediate, 70–80% of extensive and 3–5% of ultra-rapid metabolisers [26]. These genetically determined metabolic phenotypes result in different plasma concentrations of the drugs, from almost toxic levels in poor metabolisers to much below therapeutic levels in the ultra-rapid group. To date pharmacogenetic studies on response to AChEI treatment in AD are discrepant, partly due to different number of patients included, follow-up periods and definition of responders vs non-responders. Ten studies on patient populations ranging from 27 to 396 individuals treated with either donepezil, galantamine or rivastigmine were performed analysing treatment response for different phenotypes of cytochromes, mostly CYP2D6 [20]. A study investigating the effects of 16 functional polymorphisms of CYP2D6 on treatment effect in 57 AD patients treated with donepezil reported significantly higher frequencies of gene variants in responders that contribute to decreased or absent enzyme activity [27]. An Italian prospective study that included 171 patients treated with one of the three AChEIs, however, found no effect of different CYP2D6 and BChE genotypes after 1 year of treatment, irrespective of the medication used [28].

The number of published scientific studies on the influence of different genotypes of cholinergic markers (AChE, BChE and choline acetyltransferase) is growing. The BChE genotype affected treatment effect in both rivastigmine and memantine add-on therapy [29]. A deleterious effect of the BChE-K variant in donepezil treatment of MCI over 3 years was reported in a case–control study [30]. The interaction between the BChE-K genotype and donepezil response on cognitive function in this study was significantly associated with the duration of treatment. Furthermore, homozygous BChE-K carriers displayed a steeper cognitive decline on Mini-Mental State Examination (MMSE) and Clinical Dementia Rating—Sum of Boxes in donepezil-treated subjects carrying APOE-ε4 allele.

A possible explanation is that parallel pharmacological inhibition of AChE by donepezil treatment and inhibition of BChE due to polymorphism in BChE-K-variant of the enzyme cause toxic overload of acetylcholine [31, 32]. Thus, BChE genotyping represents a promising tool in selecting non-responders for AChEI therapy when eventual treatment of AD patients with a prodromal phase of the disease is considered on a case-by-case basis.

The APOE-ε4 allele is associated with an increased risk for developing late-onset sporadic AD. The majority of RCTs, three performed with donepezil, three with galantamine and two with rivastigmine (n = 2462 patients with AD), reported no influence of the apolipoprotein E (APOE) genotype on treatment response [20]. In one study on the effects of long-term treatment with donepezil in 40 patients, APOE-ε4 carriers demonstrated a poorer response on the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-cog) score after 3 years therapy [33]. In a case–control study on 81 patients, in contrast, after 12–16 months of treatment, there was a better response in specific cognitive domains of attention and memory and on MMSE in APOE-ε4 carriers [34].

Although APOE polymorphism does not seem to have an independent effect on AChEI clinical response, patients with the APOE-ε4 and CYP2D6 genotype with decreased function alleles demonstrated an increased frequency of treatment non-response [35].

Models built on the likely beneficial or detrimental effect of long-term AChEI treatment, incorporating relevant modifying factors such as age, sex and BuChE-K and APOE-ε4 polymorphism were suggested [36]. This approach might optimise treatment outcomes in future but it does not presently guide the therapeutic decisions of clinicians. With respect to optimising treatment efficacy, more complex, different neurodegenerative phenotypes will likely be defined in the future based on genetic and biomarker profiles.

Translation of Clinical Trial Outcomes to Relevant Benefits in Clinical Practice

A large number of RCTs were performed with AChEIs to evaluate their efficacy, usually against placebo treatment in AD (Table 5.1). How long trials lasted was based on their outcomes: 6–12 months if symptom improvement was intended or 18–24 months if modification of clinical course was expected [37]. Three-month trials were considered too short to demonstrate a clinically meaningful effect [37]. The most relevant clinical outcomes in the RCTs are improvement in cognitive performance, various aspects of activities of daily living (ADL), severity rating of the disease and the clinician's global impression of change compared to baseline performance [38]. Outcomes across different domains in RCTs with patients with AD are quantified by representative scales, such as: MMSE [39] and ADAS-Cog [40] for global and domain-specific cognitive status; Disability Assessment for Dementia Scale [41] and Progressive Deterioration Scale [42] for ADL; Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) [43] and Gottfries-Bråne-Steen Scale [44] for global clinical state; and Neuropsychiatric Inventory (NPI) [45] for neuropsychiatric symptoms. In trials in severe AD due to floor effect on MMSE and ADAS-Cog, the Severe Impairment Battery (SIB) [46] was used to assess cognitive decline.

A clinically relevant change is difficult to reconstruct based on minor changes or cut-off scores on individual assessment scales used across domains as trial

outcomes. The change has to be relevant for both patient and caregiver in real life. Applied in a standardised way by a clinician and caregiver, the CIBIC-Plus uses a composite score, showing if there was meaningful improvement based on criteria relevant to the patients and their carer.

Pooled data from both RCTs and observational studies make it possible to assess not only efficacy through meta-analyses but also the occurrence and profile of AEs on a large scale, not to mention differences in outcomes based on the characteristics of the patient population at baseline. For example, in the meta-database from the Alzheimer's Disease Cooperative Study and the Alzheimer's Disease Neuroimaging Initiative (n = 2793 participants) conducted from 1993 to 2012 older individuals with AD dementia enrolled in clinical trials with AChEI showed substantially less cognitive worsening measured with the ADAS-cog or MMSE than younger individuals [47].

It could be argued that the isolated small effect on cognition without effect on functional decline cannot be considered as clinically relevant. Similarly, improved or stabilised performance of ADL may not have enough of an effect to have an impact on outcomes of institutionalisation, carer impact or quality of life [48]. A systematic review and meta-analysis of the effectiveness of all commonly used pharmacological interventions to improve quality of life and well-being in people with dementia did not find consistent evidence [49]. However, only 12- to 24-week AChEI RCTs on donepezil were included in this review, since comparable trials with rivastigmine or galantamine did not report quality of life outcomes. Thus, it is still unclear whether improvements in quality of life can be expected to continue beyond short-term RCTs.

Donepezil

The main findings of RCTs on donepezil are similar in both mild to moderate and moderate to severe disease, with donepezil showing benefits compared with placebo at 26 weeks (6 months) for cognitive function, ADL and the clinician-rated global impression scales (Table 5.1). There were no differences on measures of behavioural symptoms or quality of life. AEs and withdrawal from the study were dose-related, occurring more often in patients treated with 10 and 23 mg/day [6]. Slow-release donepezil formulation of 23 mg/day did not show any advantages compared to 10 mg/day [50, 51].

Only 11% of patients with probable AD were eligible for RCTs sponsored by pharmaceutical companies due to restricted inclusion criteria [52]. Given the moderate improvements in individual domain-specific rating scales during a relatively short evaluation time in such highly selected patient populations, there was a need for more real-life outcomes in typical real-life patients with common comorbidities.

A large-scale UK-based trial called AD 2000, which did not receive any funding from pharmaceutical companies [53], was initially designed to address relevant clinical and social benefits and economic outcomes during long-term treatment.

Although the trial aimed to recruit 3000 patients referred to a memory clinic, only 566 individuals with AD and with or without cerebrovascular disease and vascular dementia (VaD) diagnosis were randomised. The trial had a modified cross-over design since patients were randomised to donepezil 5 mg/day or placebo in the initial 12 weeks and then re-randomised to 5 or 10 mg/day or placebo. The trial aimed to "determine whether donepezil produces worthwhile improvements in disability, dependency, behavioural and psychological symptoms, carers' psychological well-being, or delay in institutionalisation and if so, which patients benefit, from what dose, and for how long" [6, 53]. The first 2 years of treatment showed small improvements on tests of cognitive (MMSE) and functional (Bristol ADL Scale) ability but there was no significant delay in entry to institutional care or progression of disability, which were two primary outcome measures.

The study was criticised for various methodological limitations, for example repeated washouts that could have been associated with a loss of benefits of donepezil treatment. In addition, 48% of patients had discontinued the trial within 1 year and <20% remained by the end of the second year.

Galantamine

RCTs on galantamine that mainly included patients with mild to moderate AD [54], treatment showed significant improvements in cognition irrespective of daily dose (8–32 mg/day) or drug formulation (bi-daily vs extended-release tablets) (Table 5.1). On CIBIC, improvement or stabilisation was observed at all daily doses, except for 8 mg/day. Trials that reported changes in ADL and the Neuropsychiatric Inventory scale as outcomes showed significant treatment effect on function and behaviour [55–57]. The 6-month RCT with galantamine in patients with severe AD residing in a nursing home reported an improvement in cognitive function but there was no significant effect on ADL, which is a desirable treatment effect in advanced dementia [58]. An international, 7-month multi-centre RCT reported efficacy across all core domains in patients with comorbid AD and cerebrovascular disease [59].

Rivastigmine

A 26-week RCT reported that oral rivastigmine taken in 6 and 12 mg divided into two daily doses and a rivastigmine transdermal patch 9.5 mg/day showed benefits compared to placebo on measures of cognitive function, ADL and the physician-rated global impression of change scales, but there was no difference with respect to behavioural symptoms in mild to moderate AD (Table 5.1) [60]. Effect on cognition was rather small and thus probably not clinically relevant. Significant improvements compared to placebo on GCI scale were shown at the 26-week assessment but not at earlier time points. The transdermal patch (9.5 mg/day) seems to be as effective as peroral capsules, as suggested in the IDEAL study [61].

Memantine

In contrast to AChEI, memantine treatment led to functional improvement and reduced care dependence in severely demented patients in one initial 3-month RCT [62] and showed some beneficial effect in moderate to severe or severe AD in RCTs lasting 6 months or more (Table 5.1). Most of these studies (five RCTs listed in Table 5.1) compared the efficacy and safety of memantine (versus placebo) in patients already receiving stable treatment with donepezil [63]. Memantine was marginally superior to placebo on outcomes measuring cognitive function, ADL, behaviour and mood in mild to moderate and moderate to severe AD. A systematic review and meta-analysis of nine studies including monotherapy showed minor clinical benefits across all outcomes, including clinical global impression of improvement [64]. A meta-analysis and meta-regression of 18 RCTs involving 5004 patients reported that memantine was only slightly superior to placebo in outcomes measuring cognitive function, neuropsychiatric symptoms, global clinical assessment and discontinuation due to inefficacy, and showed no improvement in functional ability [65]. The authors concluded that the clinical relevance of memantine's efficacy in AD is doubtful. They also argued that the conclusions in several previous, optimistic meta-analyses [64, 66, 67] overlooked the relevance of the intervention effect size, which was very small across all efficacy domains [68].

Comparative Evidence of Efficacy

Head-to-head trials directly comparing efficacy of different AChEIs are sparse and limited since the majority of them used open-label design, different measurement scales for assessing outcomes and a range of fixed and flexible doses of the drugs being tested [69]. Four trials providing direct comparison of two AChEIs are frequently cited in the literature: one 52-week [70] and one 12-week open-label trial [71] compared donepezil with galantamine, and one 12-week open-label [72] and one 2-year double-blinded randomised trial [73] compared donepezil with rivastigmine. While shorter, the 12-week trials found statistically significant differences in efficacy on cognitive and functional outcomes in favour of donepezil over galantamine, while the longer 52-week trial did not find significant differences in efficacy [69]. Both trials comparing directly donepezil and rivastigmine found a similar effect on cognitive measures, while the double-blind study demonstrated even a small, statistically significant effect on functional measures in favour of rivastigmine over donepezil. Regarding positive effect on measures of change in behaviour, donepezil was significantly better than galantamine.

A network meta-analysis is another option for comparing the efficacy of two treatments and indirectly estimates differences between the effects of two drugs tested in separate RCTs by making an inference based on their efficacy versus placebo, which is a common comparator [74].

Safety and Tolerability

Most side effects of AChEI are due to cholinergically mediated GI symptoms. Across all RCTs on AChEI the most common reasons for trial discontinuation were nausea (2–8%) and vomiting (1–5%) [75]. Transdermal administration of rivastigmine has considerably improved tolerance of the drug [76]. The meta-analysis of memantine trials found no differences between memantine and placebo for both all-cause treatment discontinuation and for treatment discontinuation due to AEs [65]. A slight reservation about this conclusion is that patients with severe AD might underreport AE, possibly leading to safety overestimation of memantine prescribed in this disease stage. Table 5.3, which summarises AEs reported in anti-dementia drug RCTs, is based on Alva and Cummings' 2008 review [75], which compiled and analysed odds ratio data on AEs listed in manufacturers' patient information leaflets for donepezil, galantamine, rivastigmine and memantine. It is worth

Table 5.3 Adverse events reported in clinical trials with anti-dementia drugs

	Significant odds ratios	Non-significant odds ratios
Donepezil	Anorexia[a], diarrhoea[a], muscle cramps, nausea[a], vomiting[a]	Abnormal dreams, accidents, arthritis, back pain, chest pain, confusion, ↑ dehydration, *depression*, dizziness, ecchymosis, eczema, emotional lability, fatigue, fever, frequent urination, *hallucinations,* headache, haemorrhage, hostility, hyperlipidaemia, hypertension, infection, insomnia, nervousness, pain, personality disorder, somnolence, syncope, urinary incontinence, weight loss
Rivastigmine		
Oral administration (capsule)	Abdominal pain, anorexia[a], anxiety, asthenia, depression, diarrhoea, dizziness[a], dyspepsia, fatigue, flatulence, headache, malaise, nausea[a], sweating, tremor, vomiting[a], weight loss	Abdominal pain, accidental trauma, aggression, confusion, constipation, eructation, hallucinations, hypertension, influenza-like symptoms, insomnia, rhinitis, syncope, urinary tract infection, vertigo
Transdermal patch	*Same AEs profile, no significant odds ratios*	
Galantamine	Anorexia[a], dizziness[a], dyspepsia, fatigue, headache, nausea[a], vomiting[a], weight loss	Abdominal pain, anaemia, bradycardia, *depression*, diarrhoea, haematuria, insomnia, rhinitis, somnolence, syncope[a], tremor, urinary tract infection
Memantine	Constipation, headache, hypertension, pain	Back pain, confusion, coughing, *dizziness, dyspnoea, fatigue,* hallucinations, somnolence, vomiting

AE adverse events, AEs reported by at least 2% of patients receiving different therapeutic dosages and occurring at least twice the frequency seen in placebo-treated patients

[a]Most frequent AEs leading to discontinuation of treatment. Italics indicate AEs with odds ratios close to marginal significance. Based on Alva and Cummings [74]

mentioning to patients that most of the common GI side effects disappear in one to a few days.

In most cases typical GI cholinomimetic AEs are mild and transient and can be reduced by longer titration to the target dose, e.g. the recommended 6-week titration of donepezil from 5 to 10 mg/day. While donepezil does not have to be taken with food to reduce the frequency of GI AEs, it is recommended that galantamine and rivastigmine are administered with food. Adding anti-emetic medication and adequate fluid intake can ease nausea, which in a minority of patients taking galantamine, and even donepezil, was experienced for more than a week. To avoid nausea, donepezil is usually prescribed for the night. However, if lucid dreams develop, the patient is advised to take donepezil in the morning.

Both donepezil and galantamine treatment may reduce rapid eye movement (REM) sleep latency and lead to decreased slow-wave sleep [77]. Insomnia in RCTs was two to threefold more frequent in patients treated with donepezil than in those on placebo. Rivastigmine increases REM density and does not affect REM sleep latency. Lack of sleep was reported in patients treated with rivastigmine diagnosed with AD, dementia with Lewy bodies (DLB) or Parkinson's disease dementia (PDD) [78].

While AEs leading to discontinuation in RCTs were similar for both oral and transdermal administration of rivastigmine, their safety and tolerability profiles are different. The 9.5 mg/24 h rivastigmine transdermal patch had similar efficacy to the rivastigmine capsule (12 mg/day), with one-third of the incidence of GI side effects [11].

Interestingly, skin irritation related to the rivastigmine patch had low incidence in clinical trials, was not related to the dose and could be avoided by omitting application of the patch on the same site within 14 days. In clinical practice common notification of skin irritation is often related to various manufactures and differences in adhesive substances. Low body weight is a risk factor for experiencing more severe AEs, particularly the GI profile. Body weight of less than 50 kg is a warning sign that the patient will probably discontinue treatment with either rivastigmine capsules or patch due to AEs. Thus, weight monitoring during treatment is obligatory, and this refers to all compounds in the AChEI class. Frail older patients risk developing slight nausea and subsequent loss of appetite that may continue unnoticed for some time, resulting in weight loss over a longer period.

In the FDA Adverse Event Reporting System database serious AEs associated with AChEI are rhabdomyolysis, convulsions, falls, loss of consciousness, syncope, pneumonia and death. Other severe complications are increased gastric acid secretion, GI bleeding, urinary obstruction, deterioration of symptoms of asthma or obstructive pulmonary disease, seizures and exacerbation of extrapyramidal symptoms in Parkinsonism.

When data from unpublished studies on the use of galantamine in people with MCI at risk of developing AD were pooled, researchers found a significantly higher rate of unexplained death in the patient group treated with active drugs [54]. The studies combined included 2048 people >50 years of age with MCI. The difference

in death rates between the drug groups and the placebo became apparent within the first 3 months of treatment of patients with MCI, whereas in placebo-controlled studies of up to 6 months among patients with dementia, death rates did not differ between galantamine and placebo [79, 80]. The deaths in the galantamine MCI trials were mostly due to cerebrovascular or cardiovascular causes.

In a real-life setting it is important to be aware of frailty, comorbidities and polypharmacy in individual patients. In particular the physician should be aware of the vagotonic effect of AChEIs on sinoatrial and atrioventricular nodes causing bradycardia and heart block. A population-based study showed that recent initiation of cholinesterase inhibitors was associated with approximately a doubling of the risk of hospitalisation for bradycardia [81]. Absolute contraindications to AChEI are second or third-degree heart block in an unpaced patient; QT prolongation; and bradycardia <50 bpm. Beta-blockers are commonly prescribed drugs, and AChEIs should be prescribed cautiously if the pulse rate is between 50 and 60 bpm, even in an asymptomatic patient.

Memantine is well tolerated, but dose adjustments are needed in more severe renal impairment. AEs could be provoked by alkalinisation of the urine and therefore sodium bicarbonate and carbonic anhydrase inhibitors should be avoided.

Open-label extension and observational studies have reported good tolerability with prolonged memantine therapy, although there is a substantial dropout and survivor bias [82, 83], just as there is a risk confusion and/or having hallucinations.

Possible Beneficial Effects of AChEIs on Comorbidities in AD Patients

Evidence in the literature indicates that AChEIs can also have a beneficial effect on comorbidities as well as reduce cardiac morbidity and mortality in AD patients [84]. While bradycardia is a non-favourable and potentially serious side effect of AChEI treatment, particularly during treatment with donepezil [85], AChEIs can slow the heart rate in patients with atrial fibrillation and other causes of tachycardia. A number of studies reported a possible cardio-protective effect of AChEI [86]. A cohort study with 7073 patients from the Swedish Dementia Registry found, after accounting for confounders, that patients with AD or mixed dementia who used AChEI had a 34% lower risk of either myocardial infarction or death compared to those who did not [87]. AChEI can improve GI motility and reduce the need for laxatives in the elderly population with AD. An increase in parasympathetic innervation to the eye during AChEI therapy can reduce intraocular pressure in comorbid glaucoma in patients with AD. Furthermore dry-mouth and atonic bladder can benefit from AChEI treatment in this patient population. However, evidence from RCTs is lacking and is mostly based on real-life observational and case studies in patients who are not usually recruited in trials [84]. Nevertheless, this puts emphasis on the importance of monitoring comorbidities, polypharmacy and adjusting treatment with other drugs if a pleiotropic effect of AChEI is expected.

Treatment Efficacy Beyond the AD

Lewy body dementia (LBD) is the second most common form of neurodegenerative dementia after AD. It includes dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). Similar to patients with AD, patients with LBD show marked cholinergic deficits, but the deficits are more severe in LBD compared to AD and occur earlier in the course of the disease. Six RCTs examining LBD and cognitive impairment with no dementia in Parkinson's disease (CIND-PD) that included 1236 patients showed a positive impact on global assessment, cognitive function and neuropsychiatric symptoms such as hallucinations, apathy, anxiety and sleep disorders, and on ADL rating scales [88]. Among studies included in this meta-analysis donepezil was used as intervention drug in three studies with PDD and one with CIND-PD, while rivastigmine was used in one study with PDD and one with DLB patients. Two 24-week RCTs using memantine in a mixed study population of both DLB and PDD patients showed a significant benefit overall on clinical global impression of change but could not demonstrate a consistent pattern of treatment response in clinical subtypes of LBD with regard to cognition and non-cognitive neuropsychiatric symptoms [89, 90]. Both 24-week trials reported that memantine was well tolerated. However, there are case reports of severe states of confusion in conjunction with the introduction of memantine in patients with LBD [91, 92].

A large-scale UK study in Oxfordshire that monitored treatment with AChEI collected over 4 years data on 1250 patients, supplementing the data with an examination of retrospective case notes [93]. Patients were reassessed after a mean period of 4 months to evaluate clinical and cognitive response to therapy. The study defined clinical response as improvement sufficient to merit continuation of therapy, while an MMSE improvement of two or more points was defined as cognitive response. Patients with DLB and PDD had a better clinical and cognitive response compared to patients with AD. Cognitive but not clinical response was more likely in patients with moderate dementia than in those with mild dementia.

Vascular cognitive impairment (VCI) covers a range of cognitive and behavioural changes associated with vascular pathology. Evaluating the treatment effect using one common test battery is difficult in an etiologically heterogeneous patient group that includes both small- and large-vessel disease, either cortical or subcortical strategic infarctions, comorbidity with AD pathology (i.e. mixed dementia) or LBD. All three AChEI drugs and memantine were evaluated for their effects in vascular cognitive impairment diagnosed according to the NINDS-AIREN criteria [59, 94–97]. Only slight cognitive improvements were reported for donepezil, galantamine and memantine treatment in vascular cognitive impairment. There was evidence that in mixed dementia, galantamine could improve both cognition and global functioning [59, 95]. Two 6-month RCTs using galantamine in patients with both AD and VaD that included 1378 participants had a significantly higher patient dropout rate, mainly due to GI side effects. A meta-analysis conducted by Kavirajan and Schneider [98] included

placebo-controlled RCTs with all three AChEI and memantine in VaD. They concluded that current anti-dementia treatment led to small benefits in cognition of uncertain clinical significance in patients with mild to moderate VaD. In post-hoc analyses of the original RCTs, donepezil and galantamine showed greater improvement in patients with cortical and multiple territorial lesions compared to those with subcortical lesions.

Delirium or confusion is frequent in elderly, cognitively impaired patients, and it is hypothesised that it could be induced by a lack of acetylcholine in the brain. An open-label 24-month study of 246 patients aimed to determine whether rivastigmine had any effect on delirium in VaD [99] suggested that rivastigmine may help reduce the frequency of delirium episodes and help shorten their duration.

A hypothesis that treatment with AChEI could result in clinical improvement in some rare dementias associated with neurological conditions was tested in eight 12- to 24-week RCTs with 567 participants who received ether an active drug or placebo [100]. One study with donepezil and one with rivastigmine treatment were performed on dementia due to Huntington's disease, one study included patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leuko-encephalopathy (CADASIL) treated with donepezil, galantamine was applied in one study on frontotemporal dementia, two studies evaluated donepezil and two rivastigmine in multiple sclerosis. One 6-week RCT on donepezil was performed in progressive supranuclear palsy [101]. No firm evidence can be drawn from these trials since the sample size is small and the effect on outcomes is either small or too insufficient to be considered as clinically relevant. In four trials that included patients with multiple sclerosis, the effect of AChEI on cognitive function was observed indirectly in the clinician's impression of cognitive change in three of the four trials [100]. In one RCT that included patients with CADASIL there was a beneficial effect on measures of cognitive functions [102]. An open-label study in frontotemporal dementia reported that patients treated with rivastigmine were less behaviourally impaired and that caregiver burden was reduced after 12 months of treatment [103]. In the progressive supranuclear palsy trial using donepezil, patients' memory test scores improved, whereas their ADL and mobility scores significantly worsened [101].

AChEIs in chronic traumatic brain injury due to post-traumatic cognitive impairments, particularly memory impairments, have also been evaluated in a short-term RCT with rivastigmine [104]. There was only a weak trend favouring rivastigmine in computerised neuropsychological testing but not in the standardised clinical interviews used to assess the outcome. Interestingly, the patients with more severe injuries, possibly also showing significant focal lesions and without the APOE-ε4 genotype, were most likely to respond.

Four additional RCTs evaluated donepezil and galantamine as adjunctive therapy for depression in non-demented elderly, but there was no benefit in terms of cognitive outcomes or improvement of depressive symptoms [105]. One study even reported that there was increased depression recurrence when depressed patients in remission were treated with donepezil [106].

Health-Economic Issues

Health technology assessment agencies assess the effectiveness or cost-effectiveness of drugs approved for AD from various perspectives, such as those of clinicians, patients and their representatives, drug companies, researchers and public funding and healthcare resources [107]. The cost-effectiveness of current anti-dementia drugs is difficult to assess since there are either small or non-existing benefits in terms of functional improvement, and there is no disease-modifying effect. Furthermore, outcomes driving decision-making are mainly based on clinical scales that are questioned in terms of their relevance for patients and their caregivers. Economic modelling addresses these challenges, including resource use, healthcare costs and quality-adjusted life years of patients [108].

Evidence weighing clinical effectiveness versus cost-effectiveness is also needed to guide the reimbursement of payors. The main issue regarding cost-effectiveness of AChEI prescription is not drug costs per se, but the impact across different sectors such as delay to the institutional care [109].

A study that attracted a great deal of attention in this context was the UK Donepezil and Memantine in moderate to severe AD (DOMINO-AD) study in patients with an MMSE score of 5–13 who were on a stable dose of long-term donepezil treatment. These patients were randomised in four arms: continuation of donepezil, discontinuation, change to memantine or addition of memantine. Over 12 months, groups treated with donepezil or memantine in mono or combination therapy showed cognitive and functional benefits [110]. Secondary and post-hoc analyses of the data from the DOMINO-AD study showed that treatment with donepezil but not memantine monotherapy may delay admission to residential and nursing home care by up to 6 months [111, 112].

State-of-the-Art Management: Key Issues in Clinical Practice

When to Start?

Intuitively, the treatment should be beneficial if started early in the course of the disease. This means that hypothetically the best target populations are symptomatic individuals at high risk of developing AD but without advanced cognitive impairment or manifest dementia and who still have functional cholinergic synapses, even in the presence of wide-spread molecular pathology of the disease. However, there is no evidence to suggest that AChEI and memantine efficacy is dependent on the presence of amyloid pathology, as all of the RCTs were conducted before biomarkers of amyloid beta (Aβ)-42 pathology were widely available and thus could not be included in large-scale RCTs.

A Cochrane systematic review analysed the results of AChEI treatment for MCI in nine studies that included 5149 individuals with MCI [113]. The authors performed a meta-analysis of the three studies that were comparable that reported on conversion to dementia and none of them provided strong evidence of a beneficial

effect of AChEI (donepezil and galantamine) on the progression to dementia at 1, 2 or 3 years [114, 115]. Apart from conversion to dementia, there was no effect on the cognitive test scores used as outcome measures either. All nine studies from the Cochrane review reported a significantly higher frequency of adverse drug reaction as well as higher dropout rate in the active drug arm, with the highest rate of discontinuation occurring early on.

Early RCTs with AChEI in MCI recruited an extremely heterogeneous group of patients based on clinical definition and, while they certainly included some patients with a neurodegenerative process consistent with AD, they probably also included many patients who would not decline over time and who remained stable cognitively irrespective of any intervention.

In clinical settings clinicians meet patients with symptoms consistent with early or prodromal AD, such as individuals with MCI or those with persistent subjective cognitive decline [116, 117]. Occasionally, even only "worried well" people without any symptoms of the disease ask for a full assessment and in case of biomarker-positive findings they expect treatment with currently marketed drugs for dementia due to AD. However, do these individuals benefit from treatment usually prescribed in subjects with AD dementia? Is it ethical to treat an individual who has no predictable trajectory of decline in terms of clinically manifesting AD dementia?

Two logistic regression models including demographic, clinical and imaging test information with and without cerebrospinal fluid AD biomarkers demonstrated in a multi-centre European study that an estimate of the individual person's risk of progression from MCI to dementia the 26 months the study lasted can be improved in 65% of subjects by inclusion of cerebrospinal fluid AD biomarkers in addition to the recommended standard assessment battery with clinical and imaging tests [118].

Biomarker-based preclinical detection of AD has opened a debate on how early during the course of the disease treatment should be initiated given the uncertainty of clinical progression [119, 120]. In a recent European Alzheimer's Disease Consortium survey 23.6% of physicians offer AChEI treatment to individuals with MCI, while 50% of respondents seldom or never treat subjects with MCI [121].

A 2015 online survey of 102 members of the European Academy of Neurology and the European Alzheimer's Disease Consortium found that over 70% of the physicians considered that a biomarker-based diagnosis of prodromal AD/MCI due to AD had added value in terms of the MCI diagnosis [122]. Among the respondents 36% prescribed AChEI routinely and 39% sometimes.

At the moment no regulatory agencies recommend treatment of prodromal AD or MCI with either AChEI or memantine [123].

Who Should Prescribe the Treatment?

AChEIs are mostly prescribed by secondary care medical specialists, such as psychiatrists, geriatricians and neurologists, depending on healthcare organisation in different countries. Usually, a dementia specialist does the diagnostic disclosure in the very early stage of the disease because the diagnosis of prodromal AD (MCI due

to AD) is dependent on biomarkers [124]. Therefore, careful counselling throughout the diagnostic process [125], individual approach to treatment initiation and adequate follow-up on AEs and the treatment effect are of utmost importance [122].

AChEI treatment comprises two stages, dose escalation to the clinically effective dose, usually during the first 4 weeks, and then the maintenance phase or sustained treatment with the optimal therapeutic dose. This regime requires frequent monitoring of AEs with escalation of AChEI dose, which can be monitored by specialist nurses on staff at the memory clinic who are trained and experienced in establishing close contact with both a patient and a caregiver.

In most countries in Europe, primary care physicians with expertise in diagnosing and treating AD can also prescribe AChEIs. However, patients with MCI/prodromal, early-onset disease and atypical clinical presentations of AD should be reviewed regularly at the specialist level regardless of whether AChEI treatment or treatment with memantine is initiated. Late-onset sporadic AD cases can either be recommended by a specialist for initiation of AChEI treatment in primary care or the treatment can be initiated by a specialist and transferred to primary care once the patient is stabilised on the optimal maintenance dose.

When to Switch or Combine?

Comparative trials could not demonstrate a consistent significant difference in efficacy between the three currently marketed AChEIs [126]. Frequency and type of AEs seem to be the main difference across the various AChEIs.

Switching between AChEIs is called for when one specific AChEI is not tolerated. It is known that up to 50% of patients can tolerate another AChEI and also show a benefit from continued treatment [127]. In clinical practice the most common scenario is a switch from oral donepezil, galantamine or rivastigmine to the rivastigmine patch. A multi-centre open-label Japanese study investigated the efficacy and safety of switching to the rivastigmine transdermal patch in patients with AD who had a poor response to or experienced difficulty in continuing donepezil or galantamine [128]. After 8 weeks in the titration period and 16 weeks in a maintenance period, MMSE scores were unchanged, mainly in the patients in a mild stage of the disease. In total, 30.5% of patients showed local skin irritation, 22.0% in the titration period, and in 10.2% in the maintenance period.

Due to its short half-time, a break of more than 3 days in rivastigmine treatment requires starting with an oral or transdermal dose of 1.5 mg twice daily or 4.6 mg/24 h, with subsequent re-titration after 3–4 weeks. When switching from oral to transdermal administration, the patch should be applied on the day following the last oral dose: (a) from a 3–6-mg oral daily dose to 4.6 mg/24-hour patch; (b) from a stable 9-mg oral daily dose to 9.5 mg/24-h patch; and (c) if a 9 mg oral dose was not stable or well tolerated, switching to a 4.6 mg/24-h patch is recommended.

When to End Treatment?

There is still no universal recommendation about the termination of AChEI treatment once the disease reaches advanced stages, particularly when the patient moves to residential care. The rule of thumb is to reduce overall polypharmacy in frail people with advanced dementia or those in palliative care, since an already modest therapeutic effect on cognition and function fades. Furthermore frequency of AEs increases in the frail elderly patient population [81, 129]. On the other hand, patients' caregivers and relatives might insist on continued treatment as an indicator of their persistent loving care for the patient and a remaining hope for some treatment benefit. Most AChEIs are available in a generic form and thus affordable, but cost of questionably beneficial long-term treatment in patients with advanced dementia remains an issue.

A meta-analysis summarised five RCTs on the discontinuation of AChEIs in outpatients with possible or probable AD [130]. An additional RCT examined discontinuation among institutionalised patients with probable moderate to severe AD [131]. Due to various designs and outcomes it was difficult to draw general conclusions about the discontinuation of the treatment. While outpatient studies reported poorer cognitive outcomes among those who discontinued AChEIs, the inpatient study did not report a significant difference between continuation and discontinuation. A recent systematic review of practice guidelines and recommendations on the discontinuation of AChEI in dementia reported that 11 out of the 16 professional guidelines examined recommended discontinuation under specific circumstances, while of the remaining five, three offered no recommendation regarding discontinuation and two recommended against discontinuing AChEI treatment [132]. Even the guidelines that advocate discontinuation leave the decision to the clinician, who should weigh cost and benefit with regard to lack of treatment response or loss of treatment effectiveness, side effects or AEs, issues with patient/caregiver compliance, severity of cognitive and/or functional impairment, behavioural disturbances, overall medical condition, institutionalisation and the family or caregiver's preferences. The Canadian guidelines operationalised the decision to discontinue and recommended stopping treatment in patients with accelerated decline over 6 months, as measured by a decrease of three or more points on MMSE [133]. On the other hand, the UK recommendation approaches MMSE cut-offs with caution, instead suggesting that the level of overall disease severity should be considered [134].

In summary, there is no strict, evidence-based algorithm or standardised recommendations in terms of duration or the discontinuation of treatment. The sound judgement of a clinician and common sense indicate that an institutionalised patient who makes the transition from active to end of life care, who cannot interact meaningfully with others and who cannot perform basic ADLs will not benefit from continued treatment with AChEI.

Table 5.4 Level of evidence and strength of recommendation.

	AD	LBD	Mixed dementia	VaD	FTD	MCI
AChEI	I A	I A	I A	I A	I A	I A
• *Donepezil*	√	√	√	×	×	×
• *Rivastigmine*	√	√	√	×	×	×
• *Galantamine*	√		√	×	×	×
Memantine	I A	I B	I B	I A	I A	I A
	√	√	√	×	×	×
Combination Therapy	I B					
	√					

AD Alzheimer's disease, *LBD* Lewy body dementia, *VaD* vascular dementia, *FTD* frontotemporal dementia, *MCI* mild cognitive impairment, *AChEI* acetylcholinesterase inhibitor, I A: recommendation (A) is directly based on evidence from meta-analysis or at least one large good-quality RCT (I); I B: recommendation (B) is based on evidence from small, non-replicated RCTs or at least one controlled study with randomisation (II) or extrapolated data from evidence level I; √: treatment recommended; ×: treatment not recommended. Based on O'Brien et al. [122]

Regulatory Recommendations

The strength of treatment recommendation for clinical practice is derived from four categories of evidence for causal relationships and treatment according to standard criteria [123]. Table 5.4 provides a state-of-the-art overview of strength of recommendations for clinical practice based on a review of guidelines published by European regulatory bodies [123, 135, 136].

Future Treatments and How Close Are They?

Intervention in amyloid and/or tau processing is the mainstream of research towards disease-modifying treatments, some of which have reached phase-III clinical trials.

In parallel, new diagnostic research guidelines for AD recommend enrichment of study populations for clinical trials in prodromal AD by including Aβ42-positive biomarkers besides the amnestic MCI phenotype [137]. The dynamics of biomarker changes are also included in trial outcomes of disease-modifying interventions [37].

Many attempts have been made to reduce the burden of Aβ aggregates that form the intraparenchymal senile plaques. The large majority of trials are immunotherapy based, i.e. they use antibodies directed against the fibrils forming the senile plaques. Most trials use passive immunotherapy, where antibodies to Aβ are formed in mice, humanised and given intravenously to patients every 2–4 weeks.

Passively administered human IgG1 monoclonal antibody, aducanumab (BIIB037) was originally derived from healthy elderly donors without any cognitive problems. This antibody binds aggregated forms of Aβ, but not to monomers. In successful phase-IIB studies, aducanumab was shown to remove amyloid from the brain and to slow cognitive decline in patients with mild or prodromal AD after 1 year of monthly intravenous infusions in the PRIME study [138]. Aducanumab was then directly tested in two phase-III trials, EMERGE and ENGAGE. Planned to run

for 18 months, each study enrolled more than 1600 patients but the trials were stopped in March 2019 after about half of the patients had been enrolled. The reason given was that EMERGE and ENGAGE would miss their primary endpoints. In October 2019, the company sponsoring the trials announced that the earlier interim futility analysis was wrong, and a reanalysis of a larger dataset was positive and showed that the treatment reduced cognitive decline when the highest dose 10 mg/kg populations from the two studies were merged. The company has now filed for conditional approval. Side effects, mainly amyloid-related imaging abnormalities and especially in APOE-ε4 carriers, were declared manageable. The mechanism behind these signal changes on MRIs is probably cerebral vasogenic oedema or micro-haemorrhages induced by Aβ immunotherapy [139, 140]. These AEs were observed in 37–47% of patients who received higher doses of aducanumab.

The extent of tau pathology correlates with severity of cognitive impairment and the neurofibrillary tangle pathology – as seen in tau positron emission tomography and is predictive of future brain atrophy [141]. The extraneuronal tau plays a crucial role in the propagation of tau pathology. More accessible to drugs, the extracellular pool is a promising treatment target for immunotherapy with vaccines and humanised antibodies in clinical development [142]. Other drug development programmes are pursuing tau aggregation inhibitors and molecules with other modes of action.

Different pathophysiological pathways contribute to the multifactorial nature and heterogeneity of AD, which is why it is plausible to pursue multiple targets in search of new treatments that might be more effective when combined. Simultaneous intervention in multiple pathways, such as neuroinflammation, microglial activation and lipid metabolism, together with amyloid/tau-based therapies, might be more effective than a single-target approach [143].

Instead of Summary Supplemental Cases

Case 1

A 69-year-old male is referred for cognitive assessment due to a subjectively experienced increase in memory difficulties in the last year. Highly educated, he is physically vital with an unremarkable medical history, except possible late-onset AD in his mother. He does not have any practical difficulties in daily life, including instrumental ADL, which is confirmed by his spouse, who is nonetheless concerned about her husband's memory problems.

The Montreal Cognitive Assessment test is 25/30 (loss of point for correct date and four points on delayed recall). Extended neuropsychological test battery confirms amnestic MCI profile. MRI did not reveal considerable structural brain pathology. Medial temporal atrophy was grade 1 bilaterally. DNA APOE genotype is 3/4, and in the cerebrospinal fluid there is significantly lower Aβ42, Aβ42/40 and increased p-tau and total-tau protein.

How would you explain the diagnosis and prognosis to the patient?
What decision should you take about treatment?

Case 2
An 80-year-old widow living alone has mild to moderate late-onset AD and was tolerating the initial dose of donepezil 5 mg well. During the dose escalation phase she developed GI AEs with diarrhoea and continued nausea. She has no significant polypharmacy and, in addition to donepezil, she takes levothyroxine to substitute her hypothyreosis.

What is your decision about continued treatment?

Case 3
You receive a phone call from the relatives of a former patient, an 84-year-old male diagnosed with moderate to severe AD who recently moved to residential care in a nursing home due to both functional deterioration and behavioural and psychiatric symptoms in dementia. He has increased anxiety and hallucinations and is periodically agitated. He is generally oriented to people and has preserved autonomy regarding basic ADL. The nursing home doctor told the relatives that he planned to discontinue the donepezil 10 mg that the patient had been receiving for the last 3 years and would instead introduce a low dose of atypical neuroleptics.

The relatives ask for a second opinion. What do you suggest?

Case 4
A 55-year-old female with early-onset AD diagnosed 2 years ago is treated with donepezil 10 mg, which she tolerates well. During follow-up her MMSE decreased by two points for current score of 24/30. Her husband said that the patient was seen at the emergency department 2 days ago due to an episode of unprovoked generalised epileptic seizure. Donepezil was discontinued and treatment with levetiracetam 500 mg was initiated.

The patient and caregiver would like to know if donepezil or some other anti-dementia drugs will be prescribed in the future. What is your reply?

Case Comments

Case 1

This is a highly functional individual in an early clinical phase of the disease according to the National Institute on Aging and Alzheimer's Association's biological classification of AD based on positive biomarkers of amyloid pathology and neurodegeneration [144]. The patient was seeking assessment due to subjectively

experienced memory problems, as also observed by his long-term spouse. Provide information about the MCI diagnosis and the risk of developing AD dementia. Treatment counselling should start with information about symptomatic treatment and, if they are highly motivated to do treatment, offer AChEI.

Case 2

Since the patient tolerated donepezil 5 mg, a therapeutic dose, well, it should remain the target dose for at least the 4–6 months before the next clinical follow-up. Then depending on eventual deterioration, try to escalate again to 10 mg, since a tolerance for higher doses may increase with a longer titration period. If the treatment with donepezil 5 mg lacks efficacy and repeated AEs occur after the new trial with 10 mg, consider switching to another AChEI.

Case 3

The patient still has some remaining functional capacity and there is no reason to discontinue donepezil. If there is increased anxiety or agitation, add memantine or selective serotonin reuptake inhibitors, or in case of psychotic symptoms, consider a low dose of atypical/second-generation neuroleptics with regular evaluations of both efficacy and tolerance.

Case 4

Incidence of epilepsy in sporadic AD is higher than in healthy population and the relative risk of unprovoked seizures increases in patients with early-onset AD [145]. Theoretically, AChEIs might lower the seizure threshold but, based on data from drug registries, they rarely provoked seizures [146]. If the patient is put on prophylactic antiepileptic treatment, donepezil treatment can be reinitiated. Dose escalation is recommended. Continued treatment with AChEI is recommended in this patient since she seems to respond to therapy and has a stable course of the disease. Interestingly, there is experimental evidence that levetiracetam can improve cognition in AD [147].

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