Practical Pharmacology for Alzheimer's Disease

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Basic Theory of Pharmacology for Alzheimer's Disease

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Takashi Kudo

1.1 From the First Report of Alzheimer's Disease to Its Establishment as a Concept

An illness, later to be named Alzheimer's disease (AD), was first reported by the German psychiatrist Alois Alzheimer about 100 years ago (Fig. 1.1). On November 25, 1901, a 51-year-old woman named Auguste Deter (Fig. 1.2) was admitted to a municipal mental institution in Frankfurt am Main, where Alzheimer served as the department head. The letter of referral said, "The patient has suffered loss of memory, paranoia, insomnia, and a feeling of anxiety for a considerably long time. The patient is believed to be unable to deal with any kind of physical or mental labor." It all began after Mrs. Deter strongly suspected her husband of having an extramarital affair. Her memory rapidly deteriorated thereafter. When she had to carry things, she could not remember where to carry them; therefore, she wandered back and forth in her apartment. In the end, she could not remember where to put things away, so she hid them in other places. She also had the delusion that someone was trying to kill her, so she would scream for hours. Alzheimer, who was exploring the anatomical basis of mental illnesses, felt that a "specific disease" was concealed behind the woman's amnesia and pathological jealousy. He therefore examined her almost every day. However, she continued to become increasingly refractory to treatment; therefore, further treatment and examination became impossible. Alzheimer's writings in the medical record ended in June 1902 with "When I try to examine Auguste Deter, she refuses, as before. She cries, shouts, and even hits me. She abruptly begins crying and often continues for several hours. So I sometimes must forcibly hold her down on the bed. She can no longer eat the meals provided to her. She has developed furuncles on her back." Several months later, Alzheimer left the mental institution in Frankfurt. In April 1906, he received a phone call from the Munich Royal Psychiatric Hospital and learned that Auguste had died. He asked that her medical records and brain be sent to him. After suffering the disease for 4.5 years, she became bedridden and incontinent during the final days of her life. Auguste

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Fig. 1.1 Alois Alzheimer

Deter died at the age of 55. Upon dissecting her brain, Alzheimer confirmed that it had atrophy, and numerous nerve cells in the cerebral cortex had disappeared. He discovered extensive neurofibrillary changes (Fig. 1.3) and senile plaques (Fig. 1.4). He concluded that these two changes comprised brain changes specific to AD. On November 3, 1906, at a meeting of the South-West German Psychiatrists held in Tübingen in southern Germany, Alzheimer presented Auguste's case. This was the world's first report on AD (Okamoto 2014).

In Europe at the end of the nineteenth century, dementia referred to either senile dementia or progressive paralysis. If a patient was aged, the disease was believed to be senile dementia; at middle age, the disease was considered progressive paralysis. In other words, a disease occurring in patients aged over 50 years was classified as senile dementia, a form of intellectual impairment that occurs with age. Auguste, the first known case of AD, was first examined at the age of 51. However, she was believed to have developed symptoms of disease in her 40s; thus, she would have ordinarily been diagnosed with progressive paralysis or a mental illness. Alzheimer, who was well versed in both progressive paralysis and mental illnesses, examined

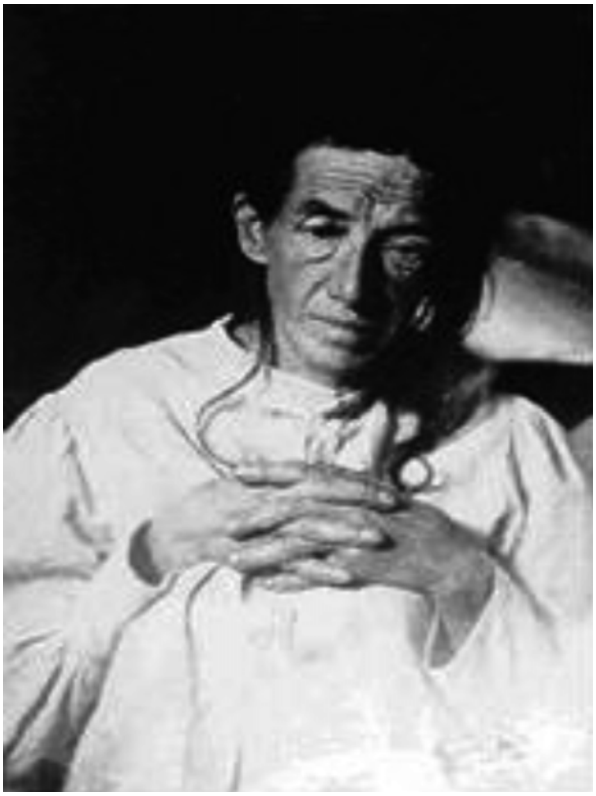

Fig. 1.2 Auguste Deter

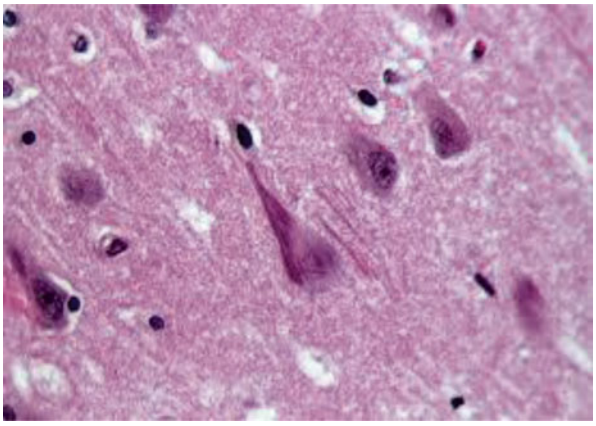

Fig. 1.3 Neurofibrillary changes (http://www.lookfordiagnosis.com)

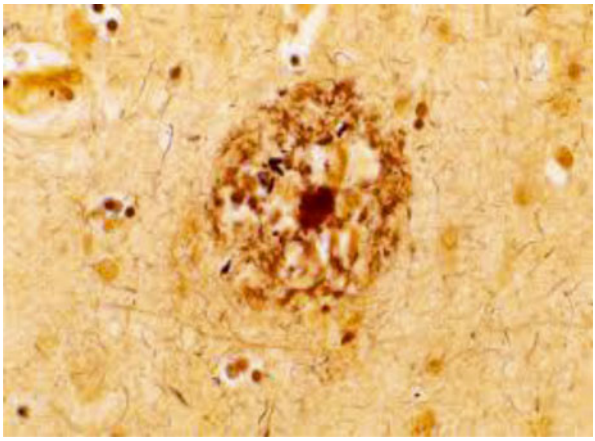

Fig. 1.4 Senile plaques (http://pixgood.com)

her symptoms, including memory disturbances, speech disruption, and a variety of other symptoms. He studied her brain after death and detected brain atrophy, senile plaques, and neurofibrillary changes. He concluded that she had a disease different from progressive paralysis or mental illness (Okamoto 2013). Emil Kraepelin named this illness "Alzheimer's disease" and described it as a presenile dementia. He stated, "The pathological findings of the brain suggest it to be a type of severe senile dementia. In view of the fact that the patient had developed the disease in her 40s', however, her disease cannot be said to be the same as senile dementia." Kraepelin believed that because senile dementia occurred because of aging, there was no boundary between dementia and normal aging of the brain. The fact that the onset was early in life led him to conclude this was a special type of dementia.

It was later revealed that the brain of patients with senile dementia had senile plaques, but the degree of neurofibrillary changes and cerebral atrophy tended to be lesser. The disease progressed slowly, as did the symptoms; therefore, AD was believed to be distinct from senile dementia. However, some declared that based on clinical and pathological data, AD and senile dementia were the same clinical entity with age of onset being the only difference. Others stressed that since dementia occurs with aging, it should be categorized as a "condition," not a disease. During the 1970s, after lengthy debates, scientists concluded that AD and senile dementia should not be considered separately but be diagnosed together as AD (Okamoto 2014).

1.2 Elucidating the Formation of Neurofibrillary Changes

Michael Kidd discovered paired helical filaments (PHFs) (Fig. 1.5), comprised of two twisted filaments, as the major structural component of neurofibrillary changes or tangles (Kidd 1963). To elucidate neurofibrillary changes, it was necessary to

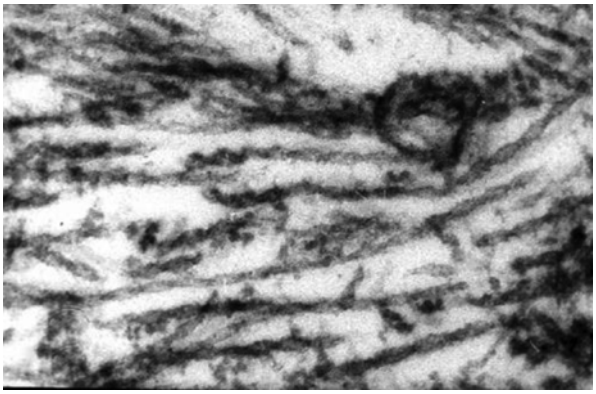

Fig. 1.5 Paired helical filaments (PHFs) (http://neuropathology-web.org)

identify the structural components of PHFs. Robert Terry et al. succeeded in doing this using a biochemical strategy (Terry et al. 1964). Khalid Iqbal and Yasuo Ihara then found that this structural component was the tau protein, one of microtubule associated proteins, with abnormal phosphorylation (Grundke-Iqbal et al. 1986; Ihara et al. 1983). Inside the nerve cells, there are proteins in the form of microtubules acting as the cytoskeletal structure. Tau stabilizes microtubules by attaching and detaching itself from them by phosphorylation level. Abnormal phosphorylation causes tau protein to separate from the microtubules. Free tau protein aggregates to form a β-sheet structure that forms PHFs, leading to neurofibrillary changes. Researchers believe that this in turn destroys microtubules and nerve cells, triggering AD.

1.3 The Acetylcholine Hypothesis

It is well known that Parkinson's disease occurs because of a reduction in levels of the neurotransmitter dopamine. Several research groups suspected that the secretion of neurotransmitters might also be involved in causing AD; therefore, they investigated the secretion of acetylcholine, a neurotransmitter involved with memory. They found that acetylcholine secretion decreased drastically in the AD brain and observed the following: (1) reduced choline acetyltransferase activity (Bartus et al. 1982), (2) a deficit of cholinergic nerves in the basal forebrain (Whitehouse et al. 1982), and (3) a reduction in nicotinic acetylcholine receptors (Sihver et al. 1999). This led to the establishment of the "acetylcholine hypothesis," which claims a reduction in acetylcholine is the cause of AD. If a person develops AD, neurofibrillary tangles occur at the early stages in brain regions originally containing large amounts of acetylcholine. This fact appeared to confirm the hypothesis. Supporters of this hypothesis believed that if a reduction in acetylcholine caused AD, then replenishing acetylcholine might help. They therefore attempted a method of treatment that involved supplementing with substances that are metabolic precursors of

acetylcholine. They believed that since providing L-DOPA, which is converted to dopamine inside the brain, to treat Parkinson's disease was proving successful, the same principle might also apply to AD. Unfortunately, the treatment was ineffective because other neurotransmitters, not just acetylcholine, were found to be decreased in the AD brain (Okamoto 2014). As a result, the acetylcholine hypothesis, which attracted enthusiastic support in the latter half of the 1970s, exited from mainstream research. Nevertheless, activation of acetylcholine is still considered an important strategy in the treatment of AD. A leading example is the use of inhibitors of acetylcholinesterase, such as tacrine, donepezil, galantamine, and rivastigmine.

1.4 The Amyloid Hypothesis

During the 1980s, AD researchers made significant progress investigating senile plaque. Senile plaques are deposits of amyloid outside nerve cells. They are also deposited in the cerebral blood vessels of patients with AD and Down syndrome. George G. Glenner at the University of California took note of this fact. He isolated amyloid from the cerebral vascular walls of subjects with AD and those with Down syndrome, purified it, and determined its amino acid sequence. In 1984, Glenner and Wong named the peptide they discovered β-amyloid (Glenner and Wong 1984). In 1985, Konrad Beyreuther et al. in Germany also revealed β-amyloid in the nuclei of senile plaques to be the same as that which Glenner had discovered (Masters et al. 1985). β-Amyloid was found to be comprised of over 40 amino acids linked together, and senile plaques were a hardened aggregation of β-amyloid. β-Amyloid was suspected to be a fragment of an even larger protein. In 1987, a group led by Jie Kang et al. in Germany identified amyloid precursor protein (APP). APP was found to be present inside brain cells, and β-amyloid was a fragment of APP cleaved by enzymes. They also found that the APP was a transmembrane protein. Moreover it was discovered that the APP gene was on chromosome 21 (Kang et al. 1987). This identification of APP resulted in the emergence of the amyloid hypothesis, which states that AD begins when there is an abnormal increase in β-amyloid (Okamoto 2014).

APP comprises about 700 amino acids. It was found that the phenomenon which causes APP fragmentation to create β-amyloid occurs very slowly even in the normal human brain (Haass et al. 1992). However, due to genetic abnormalities or other reasons, β-amyloid may end up being produced in large amounts. This led to the emergence of the "amyloid hypothesis" which states that senile plaques result from accumulation of β-amyloid in bulk outside nerve cells; this damages nerve cells and triggers neurofibrillary tangles that in turn cause neuropathy, nerve cell death, and neurologic deficits. Dementia is hypothesized to develop as a result of this series of events (Hardy and Selkoe 2002) (Fig. 1.6). However, the role of APP in human metabolism as well as the normal action of β-amyloid was unknown (Okamoto 2014).

The amyloid hypothesis has predominated AD research due to a major discovery that helped make this hypothesis rock-solid: the discovery by John Hardy in the UK

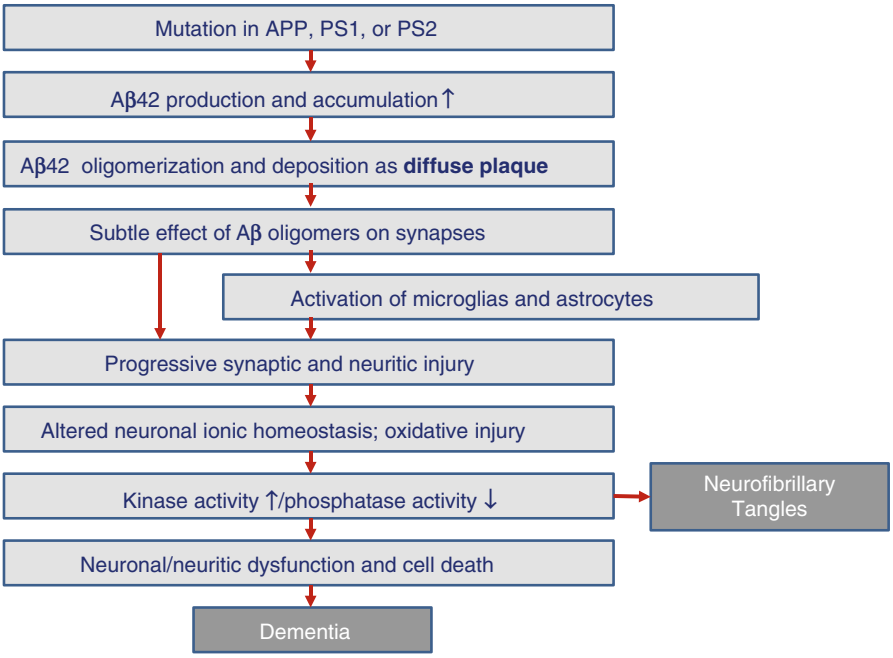

Fig. 1.6 Amyloid hypothesis (By medication of Hardy and Selkoe 2002)

of a mutation in the APP gene. Although most AD cases are not familial, approximately 10 % are of familial onset (Okamoto 2014). Many researchers have therefore attempted to identify the causal gene of familial AD and based on this research have tried to investigate the cause of general AD that develops in old age (i.e., "sporadic AD"). Hardy studied the brains of patients with familial juvenile AD and in 1991 discovered a characteristic APP gene mutation (Goate et al. 1991; Chartier-Harlin et al. 1991). Most types of β-amyloid that deposit on senile plaques have either 40 (Aβ40) or 42 amino acids (Aβ42). The type comprising 42 amino acids is especially prone to agglutination. It was shown that if the APP gene had mutations of the type Hardy discovered, then β-amyloid with 42 amino acid sequences becomes even more prone to being cleaved, making it easier for β-amyloid to deposit and form senile plaques at an early stage. Consequently nerve cells are damaged and develop neurofibrillary tangles under these conditions. The fact that a person subject to this cascade develops dementia while still young provided good evidence to support the amyloid hypothesis (Hardy and Higgins 1992).

However, even among families with familial AD, extremely few individuals had the APP gene mutation (Okamoto 2014). Researchers continued to expand their studies, strongly suspecting the presence of other causal genes. In 1995, a gene named presenilin 1 was discovered by Peter St. George-Hyslop in Canada (Sherrington et al. 1995). This was followed by the discovery of another gene which he named presenilin 2 (Sherrington et al. 1996).

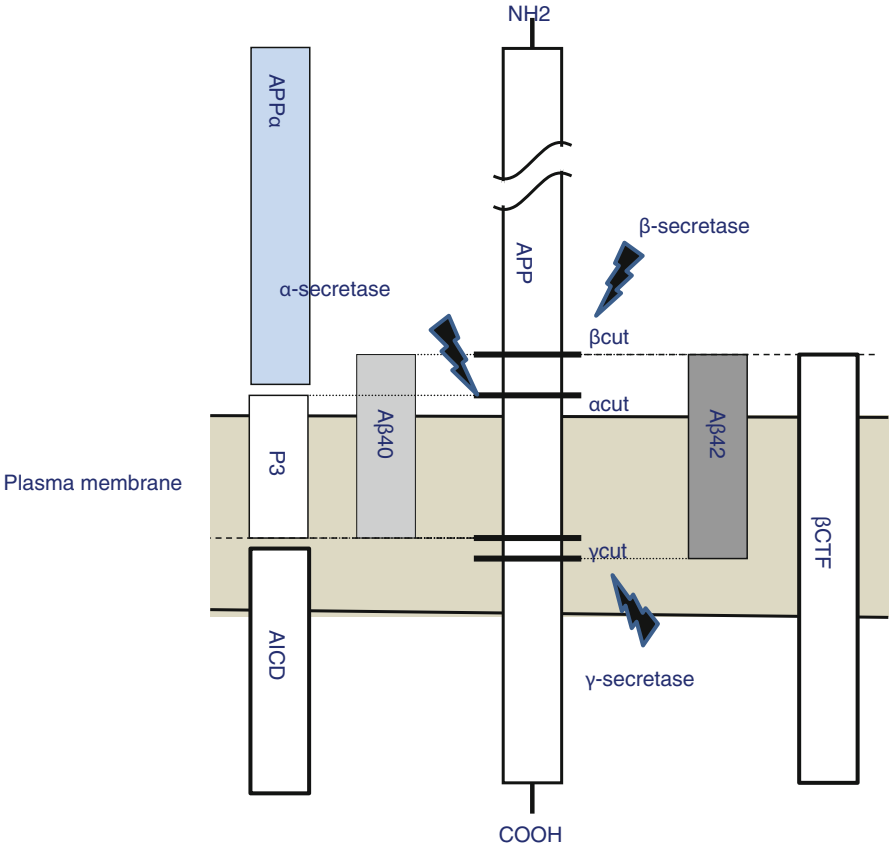

Fig. 1.7 APP processing. β-Cut by β-secretase and γ-cut by γ-secretase generate Aβ40 or Aβ42. In physiological condition, α-cut by α-secretase predominantly causes extracellular release of APPα. It is supposed that combinations of these cuttings generate P3, AICD, or βCTF

A cleavage enzyme is required at two locations to cut β-amyloid from APP. The enzyme at the first location is called β-secretase and at the second location is γ-secretase (Fig. 1.7). The two presenilins St. George-Hyslop had discovered were found to work as γ-secretases. If presenilin has a genetic mutation, it becomes liable to cleave Aβ 42. The cleavage of Aβ 42 continues to be stepped up: it accumulates, forms senile plaques, and eventually causes dementia. This process is similar to the APP genetic mutation. Therefore, mutations in the APP and two presenilin genes cause steady accumulation of β-amyloid and generate the pathology of familial AD. It was also supposed that even sporadic AD was also caused by β-amyloid accumulation as the patoent ages (Okamoto 2014). As described, the discovery of presenilin led to understanding that dementia originates with β-amyloid, further strengthening the amyloid hypothesis.

On the other hand, α-secretase which cleaves within the fragment of β-amyloid was also identified (Sisodia 1992). The α-secretase pathway is the predominant APP processing pathway. Thus, α-secretase cleavage precludes β-amyloid formation and is considered to be the non-amyloidogenic pathway of APP processing in the

physiological condition (Fig. 1.7). α-Secretase is a member of the ADAM ("a disintegrin and metalloprotease domain") family, which are expressed on the surfaces of cells. α-Secretases cleave APP to release its extracellular domain – a fragment known as APPs – into the extracellular environment (Lammich et al. 1999).

1.5 Development of Disease-Modifying Drugs (DMDs) Based on the Amyloid Hypothesis

1.5.1 Amyloid Vaccination

According to the amyloid hypothesis, one only needs to remove the amyloid that has deposited in the AD brain. The unique idea of removing amyloid by vaccination began in 1999 after Schenk et al. conducted an experiment in which they administered synthesized amyloid peptide (Aβ42) and adjuvant to AD model mice. With this amyloid vaccination, senile plaques were shown to decrease in model mice, and the formation of new senile plaques was prevented (Schenk et al. 1999). The following year, a clinical study on active immunity using an Aβ42 vaccine began. Unfortunately, the test was suspended when 6 % of the subjects suffered cerebral meningitis. One patient was diagnosed with T-cell cerebrospinal meningitis. Cerebral meningitis caused by the active immunity vaccine was believed to have an autoimmune cause, triggered by T-cells reacting to amyloid. Therefore, researchers came to consider administering a vaccine using antigens without the Aβ domain that activate T-cells, such as a passive injectable vaccine comprised of exogenously manufactured human anti-amyloid antibodies (Monsonego et al. 2003).

Regarding the effects of active immunity vaccines, it was discovered from autopsies of subjects who had died that although the volume of senile plaques decreased, progression of dementia could not have been suppressed. A long-term follow-up survey of the study subjects showed no differences from the placebo group in terms of survival rate or rate of dementia progression (Holmes et al. 2008).

At present, the focus of development has shifted to passive immunity vaccine therapy. Because anti-amyloid antibodies are administered intravenously, they react directly with amyloid deposited on the cerebrovascular wall, causing adverse events such as vascular edema. This has become a problem. The fact that the body readily produces antibodies against the monoclonal antibodies administered, and that excessive costs are incurred due to the need for repeated administration to maintain the effect of the antibodies, has also become a problem. Despite these drawbacks, massive development costs have been invested in developing amyloid vaccines; however, none of the clinical trials has come to a successful conclusion.

1.5.2 γ-/β-Secretase Inhibitors

1.5.2.1 γ-Secretase

Gamma (γ)-secretase is a membrane protein complex comprised of presenilin (PS), nicastrin, APH-1, and Pen 2. γ-Secretase is an aspartic protease with low substrate specificity. However, when cleaving Aβ from APP-βCTF, which has just β-cut,

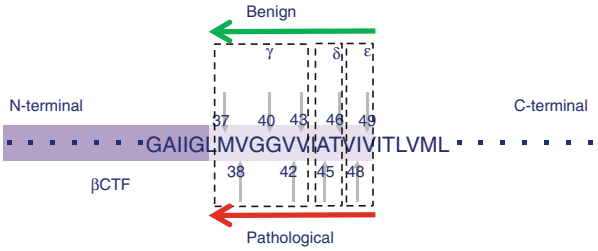

Fig. 1.8 Cleavage by γ-secretase. γ-secretase has multiple cleave sites of βCTF, i.e., ε-cleavage, δ-cleavage, and γ-cleavage. There are two pathways, i.e., the Aβ49 → 46 → 43 → 40 → 37 route and the Aβ48 → 45 → 42 → 38 route. The former is considered to be a benign pathway, and the latter, a pathological pathway

cleavage occurs predominantly at the 40th residue from the N-terminal. Ordinarily, Aβ40 accounts for 80–90 % of the total amount of Aβ produced, and Aβ42 accounts for 10–20 % (Fig. 1.7). Recent research shows Aβ40 and Aβ42 are cleaved in stages, each via separate pathways. More specifically, ε-cleavage first occurs by γ-secretase six to nine residues closer to the C-terminal on the Aβ40 or Aβ42 side than has been conventionally reported, and δ- and γ-cleavage appears to consequently occur thereafter. As shown in the Figure 1.8, Aβ is produced via two pathways, namely, the Aβ49 → 46 → 43 → 40 → 37 route and the Aβ48 → 45 → 42 → 38 route, with the latter anticipated to be more pathological (Kakuda et al. 2012) (Fig. 1.8). Aβ38 was also revealed to be produced not only from Aβ42 but also from Aβ43. These two routes are believed to cross each other (Okochi et al. 2013).

Past reports have shown there are over 90 γ-secretase substrates (Haapasalo and Kovacs 2011). Of these, Notch 1 is a substrate as important as APP. It has been established that a Notch 1 phenotype is observed in PS knockout mice (in which γ-secretase has been eliminated); it causes severe abnormalities (Shen et al. 1997). Notch signaling plays an important role in cell interactions during brain development (Artavanis-Tsakonas et al. 1999). Notch is also known to work as a proto-oncogene, tumor-suppressing molecule, in certain types of cancer (Lobry et al. 2011). In addition, Notch signaling reportedly plays an important role in the maintenance and differentiation of nerve stem cells, the structure of nerve tissues, and synaptic plasticity (Louvi and Artavanis-Tsakonas 2006; Ables et al. 2011). Therefore, impeding the physiological roles of Notch signaling by γ-secretase inhibitors (GSIs) could have serious side effects.

1.5.2.2 BACE1 (Beta-Site APP Cleaving Enzyme 1)

β-Secretase was identified as BACE1, and a knockout mouse was produced. Since no notable phenotypes were recognized in this knockout mouse, hopes arose that BACE1 inhibitors could be used as DMDs to treat AD with a minimum of side effects (Luo et al. 2001). It gradually became apparent, however, that BACE1 was required for peripheral nerve myelination by Schwann cells and correct formation of nerve axons, thus indicating a risk of side effects (Willem et al. 2006). Unlike other aspartic proteases, BACE1 has a large active site and few

hydrophobic residues. Researchers therefore point out that the molecular weight of inhibitor drugs would be high, making it difficult for them to pass through the blood–brain barrier.

1.5.2.3 Current Status and Problems of GSI Development

On August 17, 2010, Eli Lilly and Company announced they had discontinued the development of semagacestat, a nonselective GSI. This was because the preliminary-stage results of two long-term phase III clinical tests for this drug showed no suppressive effect on the advancement of mild to moderate-degree AD. In addition, the drug was accompanied by aggravation of cognitive function scores (ADAS-cog), reduced patients' abilities in daily living, and promoted skin cancer. The news was received with a huge shock, because the clinical trials involved over 3,000 patients worldwide and had been carried out with high hopes and at a huge expense. Since then, although clinical trials have been conducted on drugs with a similar mechanism of action as semagacestat, no successful evidence has been obtained as yet.

Besides the blocking of Notch signaling, nonselective GSIs are anticipated to reduce production of Aβ40, Aβ42, and the intracellular domain of APP (AICD). On the other hand, they are also anticipated to cause an increase in βCTF (the C-terminal fragment of APP that has been cleaved by β-secretase) (Fig. 1.7). Research suggests Aβ40 effectively prevents the aggregation of Aβ42 (Kim et al. 2007). Therefore, reducing Aβ40 using nonselective GSIs carries the risk of promoting amyloid deposition rather than inhibiting it. One report claims that the total volume of Aβ, rather than the Aβ42/Aβ40 ratio, defines the age of onset of familial Alzheimer's disease (FAD) (Kumar-Singh et al. 2006). There is a possibility that nonselective GSIs may reduce the total volume of Aβ, which might actually promote the pathology of AD. AICD corresponds to the intracellular domain of Notch receptor and is believed to physiologically function in controlling nerves and synapses (Zheng and Koo 2011). It can be readily assumed, therefore, that if AICD decreases because of nonselective GSI, it would lead to some form of cognitive dysfunction. Nonselective GSIs also have the potential to increase βCTF levels. Some researchers have reported that βCTF has neurotoxicity (Yankner et al. 1989); therefore, its increase may also lead to neurological disorders.

1.5.2.4 Expectations from γ-Secretase Modulators (GSMs)

It has been reported from epidemiological research into AD that certain nonsteroidal anti-inflammatory drugs (NSAIDs) specifically impede Aβ42 production, but do not block the production of Aβ40 or Notch signaling. This Aβ42-suppression effect was also shown to be independent of the cyclooxygenase (COX) inhibitory activity of NSAIDs (Weggen et al. 2001). Because these compounds "adjust" γ-secretase activity specifically at the γ-cleavage sites, they are called GSMs and are increasingly of interest as treatment drugs that do not create the adverse reactions caused by Notch inhibition.

GSMs reportedly show the following characteristics: (1) they suppress production of Aβ42, (2) promote the production of short Aβ (Aβ38 and Aβ37), (3) do not change the total Aβ or βCTF production amount, and (4) do not affect Notch

signaling (Crump et al. 2013). Based on this definition, NSAIDs such as ibuprofen, indomethacin, sulindac sulfide, flurbiprofen, and their analogs (first-generation GSM) have been tested in clinical trials. Because of their weak Aβ42-inhibitory effects and poor transferability to the brain, clinical trials did not proceed well. More recently, development has been under way on second-generation GSMs featuring improved Aβ42-inhibitory effects and better transferability to the brain.

The debate continues about the mechanism by which the effects of GSMs are manifested. Within the Aβ-production route beginning with ε-cleavage, GSMs delay the separation between Aβ42 and γ-secretase and promote cleavage to Aβ38. In contrast, PS1 mutation or GSMs with reverse actions (elevating Aβ42 in an opposite manner) can shorten the separation between this enzyme and its substrate (Okochi et al. 2013). This finding shows that simply inhibiting γ-secretase brings about a reverse effect on the treatment of AD, raising hopes for the future development of GSMs.

1.5.2.5 Reexamination of the Amyloid Cascade Hypothesis

The stagnation of clinical trials of GSIs and other DMDs questions the practicality of the amyloid cascade hypothesis as a drug discovery strategy. Even if the amyloid cascade hypothesis is correct, recent findings suggest that it takes about 20 years from the start of the appearance of amyloid and its deposition to the manifestation of dementia (Jack et al. 2010). Therefore, even if the AD is mild, amyloid has been deposited over a wide area. Therefore, it is easy to assume that even if DMDs had been administered during this period, their effects would be extremely limited. In contrast, a concept called preclinical AD is increasingly being advocated. In other words, even though symptoms of dementia may not have manifested, if amyloid abnormalities are revealed by amyloid imaging and are present in the cerebrospinal fluid, physicians are increasingly likely to identify the disease as AD and initiate treatment by aggressively prescribing DMDs (Mangialasche et al. 2010).

According to the amyloid cascade hypothesis, if the rise in Aβ levels and its deposition could be suppressed, it would be possible to treat AD. Is this really true? It has recently been shown that tau is needed for Aβ to cause neuropathy. Transgenic mice expressing mutant APP show memory and learning disabilities in a water maze. If these mice are crossed with tau knockout mice, the tau gene-defective offspring have no memory or learning disabilities. They show no differences from controls, even though amyloid has been deposited (Roberson et al. 2007). On the other hand, if fibrillized Aβ42 is injected into the brains of transgenic mice expressing frontotemporal lobar dementia FTDP-17 mutant (P301L) tau, the fibrous accumulation of tau is stepped up (Gotz et al. 2001). These animal experiments suggest Aβ associates with tau protein to advance the pathological process. Suppressing the pathology of Aβ only, using DMDs, therefore may be only part of the story.

In pathological research on AD, it has primarily been thought that the number of neurofibrillary changes (tau pathology) is related to the duration of the disease and clinical symptoms (Braak and Braak 1996). After 1998, variations in diverse tau genes were successively reported in families with dementia that essentially had tauopathies only (Lee et al. 2005). These diseases are generally referred to as

frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), revealing the existence of a mechanism by which tauopathy is clearly different from the amyloid cascade hypothesis. Thus, it is possible the development of tauopathy is more closely linked to nerve cell death than to β-amyloid, regardless of the accuracy of the amyloid cascade hypothesis that claims the formation of tauopathy takes place downstream of β-amyloid accumulation.

1.6 Paradigm Shift of the Dementia Pathology Hypothesis

1.6.1 The Pathology of Abnormal Protein Accumulation Commonly Seen in Dementia

Dementia pathologies caused by neurodegeneration are commonly explained by the mechanism of abnormal protein accumulation inside nerve cells. Until now, it has been possible to cite pathologies such as amyloidopathy, tauopathy, TDP-43 proteinopathy, α-synucleinopathy, polyglutamine disease, and prion disease. In all these diseases, it is predicted that abnormal protein is subject to phosphorylation and ubiquitination, and fibers aggregate and acquire nerve cell toxicity.

1.6.1.1 Amyloidopathy (For Details, See the Previous Section)

AD's pathological process can be explained by amyloidopathy. Aβ is a highly cohesive protein with a molecular weight of approximately 4,000 kDa; it forms senile plaques and cerebrovascular amyloids. APP is a type I transmembrane protein and is cleaved by α-secretase, β-secretase, and γ-secretase. However, Aβ is formed by phased cleavage of β-secretase and γ-secretase (Fig. 1.7). Two primary molecular species of Aβ are produced: Aβ40, which has 40 amino acid residues, and the highly cohesive Aβ42 that is two residues longer. Aβ42 deposits at an early stage and forms senile plaques, the characteristic pathological change seen in AD.

Aβ is secreted extracellularly and broken down by neprilysin (Iwata et al. 2000) and insulin-degrading enzyme. The part of the secreted Aβ then begins to form amyloid fibrils and aggregates. It either deposits in the intercellular space of the cerebral parenchyma to form senile plaques or deposits on the cerebrovascular wall and forms amyloid angiopathy. In the past, the Aβ of these insoluble aggregates was believed to be neurotoxic. More recently, however, Aβ oligomer present in soluble form, before fibrous aggregation takes place, is believed to demonstrate even stronger toxicity.

1.6.1.2 Tauopathy

The pathological process of tauopathy consists of a disease condition characterized by abnormal accumulation of tau on nerve and glial cells. It is not only seen in AD neurofibrillary changes but also in degenerative diseases such as Pick's disease, corticobasal degeneration, and progressive supranuclear palsy.

Tau, a microtubule-associated protein, promotes the formation of microtubules. It is expressed as six isoforms by selective splicing. It can be composed of

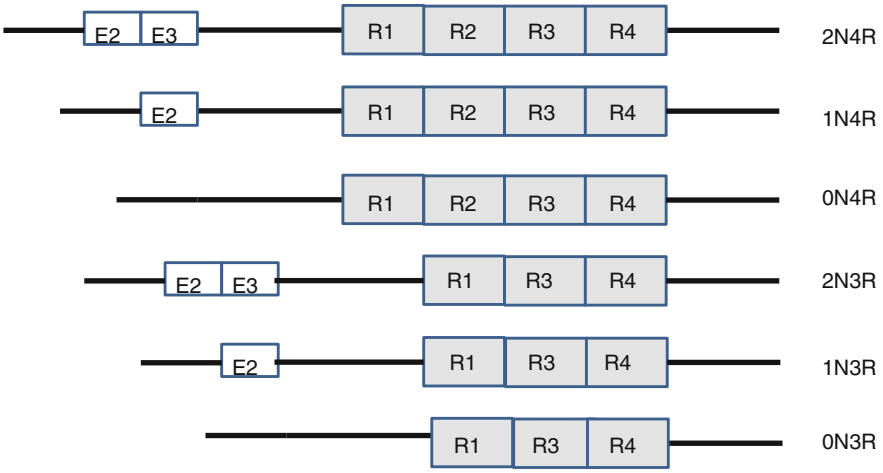

Fig. 1.9 Isoforms of tau. Six isoforms of tau are composed of three (R1, R3, and R4) or four repeat regions (R1, R2, R3, and R4), those that have exon 2 (E2) and 3 (E3), those that have exon 2 only, and those that have neither exon 2 nor 3

three (R1, R3, and R4) or four repeat regions (R1, R2, R3, and R4), those that have both exon 2 (E2) and 3 (E3), those that have E2 only, and those that have neither E2 nor E3 (Fig. 1.9). Tau bindings to microtubules are formed by these repeat regions.

Tau contains numerous potential phosphorylation sites. In solution, it does not adopt a folded structure, making it an ideal target for intracellular kinases. In fact, the polymerization and depolymerization processes seen with microtubules are caused by the phosphorylation and dephosphorylation reactions. Tau that has been excessively phosphorylated loses its microtubule-binding capabilities, making the microtubules unstable. Tau that has separated from its associated microtubules rises to high intracytoplasmic concentrations, undergoes self-polymerization, and causes neurofibrillary changes. PHFs and straight filaments, which are constituent factors of AD neurofibrillary changes, are fibrils made of excessively phosphorylated tau. Kinases related to tau phosphorylation include cyclin-dependent kinase 5 (Cdk5), glycogen synthase kinase 3 (GSK3), mitogen-activated protein kinase (MAPK), and stress-activated protein kinase (SAPK).

Accumulation of tau protein is also observed in Pick's disease, corticobasal degeneration, and progressive supranuclear palsy; therefore, these pathologies have come to be regarded together as tauopathies. There are three types of tauopathy: (1) 3-repeat type (in which insoluble 3-repeat tau predominates, such as in Pick's disease and FTDP-17), (2) 4-repeat type (insoluble 4-repeat tau predominates, such as corticobasal degeneration and progressive supranuclear palsy), and (3) 3 + 4 repeat type (mixed type such as AD and neurofibrillary change-type dementia). Many aspects of the disease specificity of tau isoforms remain unclear. However, isoforms require a set physiological ratio, and the disruption of balances may lead to disease onset. As mentioned previously, development of a

therapeutic method based on the amyloid cascade hypothesis is currently facing difficulties, suggesting the need to develop treatment drugs based on tauopathy as well.

1.6.1.3 TDP-43 Proteinopathy

The concept of frontotemporal lobar degeneration (FTLD) has been established, based on the region of the brain where neurodegeneration develops (the frontal and temporal lobes), as well as its clinical symptoms. FTLD comprises frontotemporal dementia (FTD), semantic dementia (SD), and progressive nonfluent aphasia. With the discovery of tau genetic mutations in TDP-17, it was believed that a large portion of FTLD could be explained in terms of tau abnormalities. However, a considerable number of FTLD types were shown to be characterized by tau-negative ubiquitin-positive inclusion bodies. Thus, analysis of its pathology was conducted assuming it to be FTLD-U (FTLD with tau-negative ubiquitin-positive inclusion bodies). As a result, a genetic mutation of progranulin (PGRN) was identified in familial FTLD-U linked to chromosome 17 (Cruts et al. 2006; Barker et al. 2006). Ordinarily, in neurodegenerative diseases, molecules identified as the causal genes make up the neuropathological structures. Therefore, whether PGRN comprised FTLD-U's ubiquitin-positive inclusion bodies or not was examined, but the inclusion bodies contained no PGRN. Instead, haploinsufficiency is hypothesized. For example, with PGRN mutations, mutant-type mRNA is broken down by nonsense-mediated decay and therefore does not express the amount of functional PGRN protein decreases.

Further analysis of tau-negative ubiquitin-positive inclusion bodies revealed that their major structural components consisted of TAR DNA-binding protein 43 kDa (TDP-43) (Neumann et al. 2006; Arai et al. 2006). In amyotrophic lateral sclerosis (ALS), TDP-43 was revealed to be the major structural component of ubiquitin-positive inclusion bodies. Thus, FTLD-U and ALS came to be regarded as TDP-43 proteinopathies, possessing the same cause of the disease.

TDP-43 is a type of heterogeneous nuclear ribonucleoprotein (hnRNP). Physiologically it is localized in the nucleus, binds with RNA and other hnRNP, and is involved in stabilization of RNA, selective splicing, transcription regulation, and other processes. Much remains unclear about the mechanism by which TDP-43 accumulates. A decrease in PGRN, attributable to haploinsufficiency, may influence the metabolism of TDP-43 and result in a loss of physiological function. It is currently believed that, like tau, abnormal TDP-43 that has been phosphorylated and fibrillized accumulates inside the nucleus and cell, where it causes cytotoxicity leading to neurodegeneration.

1.6.1.4 α-Synucleinopathy

Genetic mutations of α-synuclein were discovered from the analysis of familial Parkinson's disease (Polymeropoulos et al. 1997). With this as the trigger, it became clear that α-synuclein was a structural component of Lewy bodies (Spillantini et al. 1997). Therefore, Lewy body dementia, characterized by the presence of dementia, and Parkinson's disease fall into this category.

Much about the physiological function of α-synuclein remains unclear. Synaptic plasticity, transport of vesicles, and a chaperone-like function are suspected. Mutant α-synuclein either promotes coagulation and the formation of oligomers or induces instability of the protein structure (Bertoncini et al. 2005). Over 90 % of α-synuclein that accumulates in patient's brains, like other accumulated proteins, are phosphorylated at Ser129 (Fujiwara et al. 2002), with a portion of it being ubiquitinized (Hasegawa et al. 2002).

1.6.1.5 Polyglutamine Diseases

Polyglutamine diseases are those in which CAG codon repeats coding for glutamine expand, and the genetic products containing the extended polyglutamine form aggregates and ubiquitin-positive inclusion bodies inside the nucleus and cytoplasm. Huntington's disease is an autosomal dominant neurodegenerative disease. Huntingtin was identified as the causal gene, and the disease occurs as a result of the expansion of a cytosine–adenine–guanine (CAG) repeat stretch that exists in exon 1 (The Huntington's Disease Collaborative Research Group 1993). Whereas the number of normal CAG repeats ranges from 10 to 29, the number of repeats in patients with Huntington's disease expands to between 36 and 121. The CAG repeat is unstable in spermatozoa; therefore, paternally derived repeats are susceptible to expansion. Anticipation is observed, namely, the age of onset also tends to reduce with each generation.

Other polyglutamine diseases include dentatorubral-pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy, and some forms of hereditary spinocerebellar degeneration.

1.6.1.6 Prion Diseases

Normal prions (PrP^{c}) found inside the body can cause conformational alterations, acquire insolubility, and become pathological or abnormal prions (PrP^{scr}), which accumulate and cause neurodegeneration. PrP^{scr} becomes the seed and rapidly changes PrP^{c} into PrP^{scr}, speeding abnormal accumulation. Prion diseases include idiopathic (sporadic) Creutzfeldt–Jakob disease (CJD), infectious CJD, and hereditary prion disease.

Infectious CJD made it to the headlines in the past, as numerous incidents of iatrogenic CJD occurred following transplantation of human postmortem dried dura mater in brain operations. There were also cases where cows fed on cattle bone chips developed mad cow disease, and humans who reportedly ate the meat of infected cows developed variant CJD. Genetic prion disease shows autosomal dominance and is caused by PrP gene mutations. Examples include familial CJD, Gerstmann–Sträussler–Scheinker disease, and fatal familial insomnia.

1.6.2 Endoplasmic Reticulum (ER) Stress and Dementia

The results of molecular biological analyses carried out in recent years have revealed the pathology of dementia that accompanies numerous forms of neurodegeneration.

Interestingly enough, many diseases can be explained by accumulation of abnormal proteins. The dysfunction of abnormal proteins themselves, their phosphorylation, ubiquitination, and aggregation causing neurotoxicity are all commonly seen. It is clear, therefore, that measures to suppress such accumulation will lead to the establishment of comprehensive treatment methods for neurodegeneration. Further developments are eagerly awaited.

We have thus far been studying the pathology of AD from the standpoint of reactions to ER stress or the unfolded protein response (UPR). UPR is believed to be directly involved in the accumulation of abnormal protein and is becoming an increasingly important branch of neurodegenerative disease research.

1.6.2.1 Three ER Stress Reactions (UPR) (See Fig. 1.10)

The ER plays the role of a "protein assembly plant," engaging in work such as folding and posttranslation modification of secreted and membrane-forming proteins. Because it is an "assembly plant," it inevitably sees defective products, such as proteins that have been folded insufficiently or incorrectly (unfolded proteins). Intracellular stressors, such as changes in calcium dynamics, changes in oxidation–reduction conditions, excessive production of secreted proteins, glucose insufficiency, and changes in glycosylation, are called ER stress and increase the levels of unfolded proteins inside the ER. To prevent the release of these defective products, the ER possesses a quality control function, the UPR. At present, three ER stress reactions are known. The cell attempts to overcome ER stress by using these

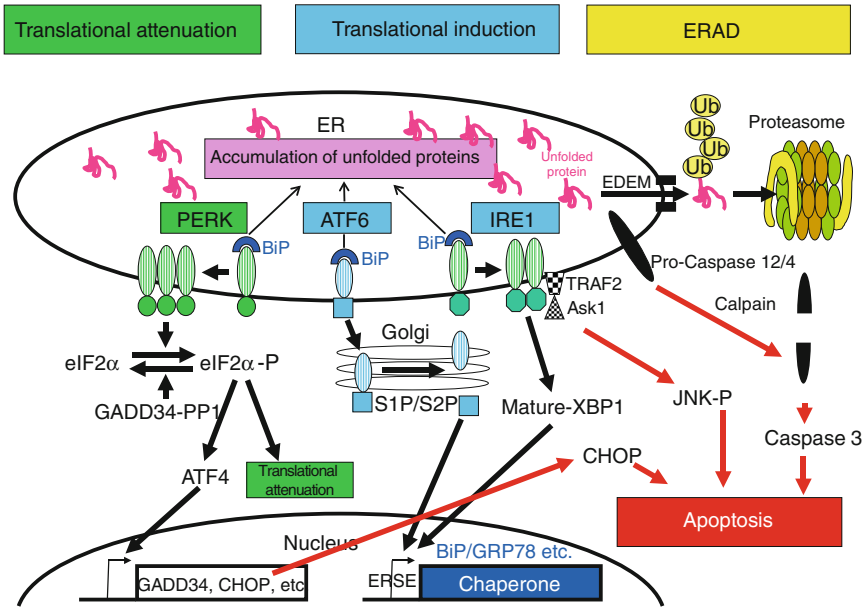

Fig. 1.10 Three ER stress reactions (UPR)

mechanisms. If the stress cannot be overcome, cells are led to the apoptosis pathway, to be described below:

1. Translational attenuation
   As the first strategy to prevent unfolded proteins from further accumulating inside the ER, the cell suppresses protein translation as a whole. This is brought about by phosphorylation of eIF2α, which is a translation initiation factor (Shi et al. 1998; Harding et al. 1999).
2. Translational induction
   As the second strategy, the cell activates intracellular signal transmission from the ER to the nucleus, which induces the expression of chaperone proteins such as BiP, calnexin, and calreticulin. These chaperone proteins either promote or rectify the folding of unfolded proteins building up inside the ER (Sidrauski et al. 1998).
3. ER-associated degradation (ERAD)
   If the unfolded proteins that have accumulated inside the ER cannot be fully processed, they are transported from the ER to the proteasome where they are broken down (Bonifacino and Weissman 1998). In the case of glycoproteins, chaperone-induced calnexin and calreticulin combine with the unfolded protein and form calnexin/calreticulin with UDP–glucose–glycoprotein glucosyltransferase (Deprez et al. 2005). Glycoproteins found in the calnexin/calreticulin cycle leave calnexin/calreticulin after mannose is cleaved by α-mannosidase I and bind with ER degradation-enhancing α-mannosidase-like protein (EDEM) to ascertain whether it is unfolded or not (Molinari et al. 2003). Glycoproteins identified by DEM as unfolded are transported from inside the ER to the cytoplasm via translocons (Lee et al. 2004) and are ubiquitinized by the E1–E2–E3 ubiquitin system and then broken down by the 26S proteasome.

1.6.2.2 ER Stress Sensor Molecules (See Fig. 1.10)

The UPR begins upon sensing the accumulation of unfolded proteins inside the ER. PERK, ATF6, and IRE1 have been reported as sensors of unfolded proteins present on the ER membrane:

1. PERK (pancreatic ER kinase or PKR-like ER kinase)
   PERK is a type-I transmembrane protein found on the ER membrane. The ER luminal region at the N-terminus is the ER stress sensor, while the C-terminus possesses serine/threonine kinase activity that phosphorylates eIF2α (Shi et al. 1998; Harding et al. 1999). PERK's stress sensor region is inactivated due to BiP binding. If ER stress occurs, unfolded protein accumulated within the ER separates BiP from PERK and causes the multimerization and autophosphorylation of PERK (Bertolotti et al. 2000). Phosphorylated PERK phosphorylates the serine at eIF2α's position 51. Phosphorylated eIF2α (eIF2α-P) inhibits the formation of the 43S initiation complex and impedes the initiation of translation (translational attenuation) (Shi et al. 1998). As a result, the production of many proteins is reduced under ER stress. In contrast, levels of the transcription

factor ATF4 are elevated and increase the transcription of specific genes (Harding et al. 2000). One such factor, GADD34, forms a complex called GADD34-PP1 with protein phosphatase 1, dephosphorylates eIF2α once again, and restores protein translation to the original state to end the ER stress reaction (Novoa et al. 2001).

2. ATF6
   ATF6 is a type II transmembrane protein also found on the ER membrane. Under a non-ER stress state, BiP binds to the inner lumen and inhibits the ER-to-Golgi transport signal (Shen et al. 2005). Under ER stress, ATF6 releases the binding of BiP, is transported to the Golgi body by vesicle transport, and is cleaved near the transmembrane region on the cytoplasm side by site-1 protease (S1P) and site-2 protease (S2P). The N-terminal region produced leaves the ER membrane, moves to the nucleus, and binds to an endoplasmic reticulum stress element, thereby promoting the induction of BiP and calreticulin (Yoshida et al. 1998).
3. IRE1
   IRE1 is another type I transmembrane-type serine/threonine kinase found on the ER membrane and possesses endoribonuclease (RNase) activity. IRE1's luminal region has high homology with that of PERK. Under nonstressed conditions, BiP is believed to bind to IRE1's luminal side. If unfolded proteins appear inside the ER, BiP separates and IRE1 forms a dimer that is phosphorylated by RNase activity. In mammalian cells, this phosphorylated IRE1 excises an intron of XBP1 mRNA, thereby causing a frame shift that induces the appearance of mature XBP1, which has a transcription-promoting factor at the C-terminus (Calfon et al. 2002; Yoshida et al. 2001). This mature XBP1 moves to the nucleus, binds with UPR elements (UPRE) on the promoter side of chaperone protein genes, and induces/guides these chaperone proteins (Tirasophon et al. 1998; Wang et al. 1998). Mature XBP1 also induces ERAD-relating factors, such as EDEM (Oda et al. 2006).

   As described, a common mechanism appears likely, in which the activation of ER stress sensors is caused by separation of BiP that was previously combined.

1.6.2.3 ER Stress and Cell Death (See Fig. 1.10)

If there is excessive or long-term ER stress not sufficiently handled by the UPR, cells undergo apoptosis in an attempt to terminate the situation:

1. Induction by CHOP
   CHOP/GADD153 (growth arrest DNA damage 153) is a transcription factor induced during the ER stress state by the ATF6 and PERK systems (Ma et al. 2002). CHOP induces DR5 (death receptor 5), activates the caspase cascade, and causes apoptosis (Yamaguchi and Wang 2004).
2. Activation of the c-JUN NH2-terminal kinases (JNK) channel
   IRE1 on the ER membrane that has been activated binds to c-Jun-N-terminal inhibitory kinase (JIK) and TRAF2. TRAF2 then activates apoptosis-signaling kinase 1 (ASK1) (Nishitoh et al. 2002). Activated ASK1 induces the activation of JNK (JNK-P) and caspases (Yoneda et al. 2001).

3. Activation of caspase 12/4
   Activation of caspase12 acts as a trigger for the ER stress-specific caspase cascade (Nakagawa et al. 2000). ER stress causes tumor necrosis factor receptor-associated factor 2 (TRAF2) to drop out from pro-caspase12 and causes it to bind to activated IRE1. Pro-caspase12, from which TRAF2 had dropped out, forms a cluster on the ER membrane and is activated (Macejak and Sarnow 1990). Pro-caspase12 is cleaved by m-calpain, activated by calcium released from the ER, and becomes activated caspase12 (Nakagawa and Yuan 2000). Caspase12 triggers the activation of caspase 3 that ultimately guides caspase 9 to cell death. Much remains unclear about the involvement of caspase 12 in apoptosis in humans, but we have identified caspase 4 as the human homolog of caspase12 (Hitomi et al. 2004).

1.6.2.4 ER Stress and PS1

PS1, the most frequent causal gene of FAD, often localizes in the ER. Therefore, we analyzed the relationship between ER stress and PS1 mutants. Nerve cells with FAD PS1 mutations were shown to be vulnerable to ER stress (Katayama et al. 1999). In these cells, chaperone induction in response to ER stress, or BiP's mRNA expression, was suppressed (Katayama et al. 1999, 2001). Moreover, IRE1, which is upstream of BiP induction, is activated by dimer formation and autophosphorylation. Therefore, when IRE1's autophosphorylation by ER stress was studied using nerve cells to which the PS1 mutant had been introduced, it was found that such autophosphorylation was delayed. In other words, PS1 mutants were shown to inhibit the UPR at the IRE1-BiP channel as a result of ER stress (Katayama et al. 2001; Yasuda et al. 2002). To study whether or not vulnerability to ER stress in PS1 mutants reflected the direct impediment of the UPR, we induced infections in PS1 mutant cells (recombinant BiP) using Semliki Forest virus and examined their vulnerability to ER stress. It was found that ER stress vulnerability in PS1 mutant cells could be rescued with the induction of BiP by the virus. It was therefore confirmed that PS1 mutants were vulnerable to ER stress, since UPR was inhibited. BiP's actual protein levels have been studied using AD brains and the brains of healthy elderly subjects. It was found that BiP had decreased in the brains of patients with FAD and decreased with sporadic AD, suggesting that disorders of the UPR form a part of AD pathology. Our studies have also shown that PS1 mutants impede systems that mediate PERK (which is another type of UPR) and ATF6. As described, PS1 mutants impede all UPRs and induce nerve cell stress vulnerability. In brains of patients with sporadic AD, levels of molecular chaperones are decreased, strongly suggesting that ER stress vulnerability is involved in AD pathology.

1.6.2.5 ER Stress and APP Processing

We found that ER stress altered the localization of amyloid precursor protein (APP) from late compartments to early compartments of the secretory pathway and decreased the level of Aβ 40 and Aβ42 release by β- and γ-cutting. Transient transfection with BiP/GRP78 also caused a shift of APP and a reduction in Ab secretion. It was revealed that the ER stress response facilitated binding of BiP/GRP78 to APP,

thereby causing it to be retained in the early compartments apart from a location suitable for the cleavages of Aβ. These findings suggest that induction of BiP/GRP78 during ER stress may be one of the regulatory mechanisms of Aβ generation (Kudo et al. 2006).

1.6.2.6 ER Stress and Tauopathy

Activation of ER stress and increased levels of phosphorylated tau were observed in the hippocampus of patients with tauopathy, suggesting that ER stress may be related to tauopathy (Nijholt et al. 2012). We show that ER stress, induced by glucose deprivation or chemicals, increases total endogenous tau protein in cultured neurons and primary cultured neurons. Under ER stress, no significant differences were observed in the transcription of tau, and no differences were observed in the translation of tau with or without the 50-untranslated region (50UTR) of tau. In contrast, the degradation rate of tau was decreased by 20 % under ER stress. ER stress reduced the binding between tau and carboxyl terminus of Hsc70-interacting protein (CHIP), ubiquitin E3 ligase for tau. These results suggest that ER stress increases total tau protein, and its mechanism is due to the decrease in the binding between tau and CHIP, which delays the degradation of tau protein through the ubiquitin–proteasome pathway. This mechanism may provide clue to treatment for tauopathy (Sakagami et al. 2013).

1.6.2.7 Therapeutic Strategy Based on ER Stress

In a screen for compounds that induce the ER-mediated chaperone BiP (immunoglobulin heavy-chain binding protein)/GRP78 (78 kDa glucose-regulated protein), we identified BiP inducer X (BIX). BIX preferentially induced BiP with slight inductions of GRP94 (94 kDa glucose-regulated protein), calreticulin, and C/EBP homologous protein. The induction of BiP mRNA by BIX was mediated by activation of ER stress response elements upstream of the BiP gene, through the ATF6 (activating transcription factor 6) pathway. Pretreatment of neuroblastoma cells with BIX reduced cell death induced by ER stress. Intracerebroventricular pretreatment with BIX reduced the area of infarction due to focal cerebral ischemia in mice. In the penumbra of BIX-treated mice, ER stress-induced apoptosis was suppressed, leading to a reduction in the number of apoptotic cells. Considering these results together, it appears that BIX induces BiP to prevent neuronal death by ER stress, suggesting that it may be a potential therapeutic agent for cerebral diseases caused by ER stress (Kudo et al. 2008).

We recently demonstrated that endoplasmic reticulum (ER) stress induces sigma-1 receptor (Sig-1R) expression through the PERK pathway, which is one of the cell's responses to ER stress. In addition, it has been demonstrated that induction of Sig-1R can repress cell death signaling. Fluvoxamine (Flv) is a selective serotonin reuptake inhibitor (SSRI) with a high affinity for Sig-1R. In the present study, we show that treatment of neuroblastoma cells with Flv induces Sig-1R expression by increasing ATF4 translation directly, through its own activation, without involvement of the PERK pathway. The Flv-mediated induction of Sig-1R prevents neuronal cell death resulting from ER stress. Moreover, Flv-induced ER stress resistance reduces the

infarct area in mice after focal cerebral ischemia. Thus, Flv, which is used frequently in clinical practice, can alleviate ER stress. This suggests that Flv could be a feasible therapy for cerebral diseases caused by ER stress (Omi et al. 2014).

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The Practical Pharmacology of Donepezil

2

Takashi Kudo

2.1 Introduction

From 1976 to 1977, three British groups established the acetylcholine (ACh) hypothesis, which claims that the activity of choline acetyltransferase (ChAT), an ACh synthase, is decreased in the brains of patients with Alzheimer's disease (AD), causing a disorder in their cholinergic system with the decline in ACh (Bowen et al. 1976; Davies and Maloney 1976; Perry et al. 1977). Consequent to this development, researchers felt that replenishing ACh might treat AD. They attempted a treatment method involving supplementation of substances that serve as raw materials for ACh synthesis. ACh synthesis was expected to be catalyzed by ChAT from choline supplied from outside the brain and acetyl CoA produced inside the brain. Therefore, a clinical trial of choline administration using Lethicin was conducted. However, the efficacy of this treatment could not be confirmed. Next, a method was contrived to increase ACh in the synaptic cleft by inhibiting ACh esterase (AChE), an ACh-degrading enzyme (Fig. 2.1). Physostigmine, an alkaloid, shows AChE inhibitory activity. A clinical research study was also reported the use of tacrine as an AChE inhibitor (Summers et al. 1986). However, these drugs received poor clinical assessments. One reason was that physostigmine is an extremely unstable compound, and the other was tacrine-induced serious liver dysfunction.

Hachiro Sugimoto of Eisai and his group also conducted drug discovery studies based on the ACh hypothesis. They used tacrine as a source for one compound. Unsurprisingly, all the synthesized derivatives showed strong toxicity, and none demonstrated any potential for commercialization. They also studied anti-hyperlipidemia drugs and discovered a certain compound that increased ACh, leading to the development of donepezil.

In Japan, phase I clinical testing of donepezil began in 1989. In the USA, the same testing began in 1991 and proceeded extremely smoothly. In November 1996, the US FDA approved donepezil for the use as an AD treatment drug. It is extremely rare for a drug to obtain approval only 8 months after application. Donepezil was approved in Europe in 1999 and received approval in Japan the same year.

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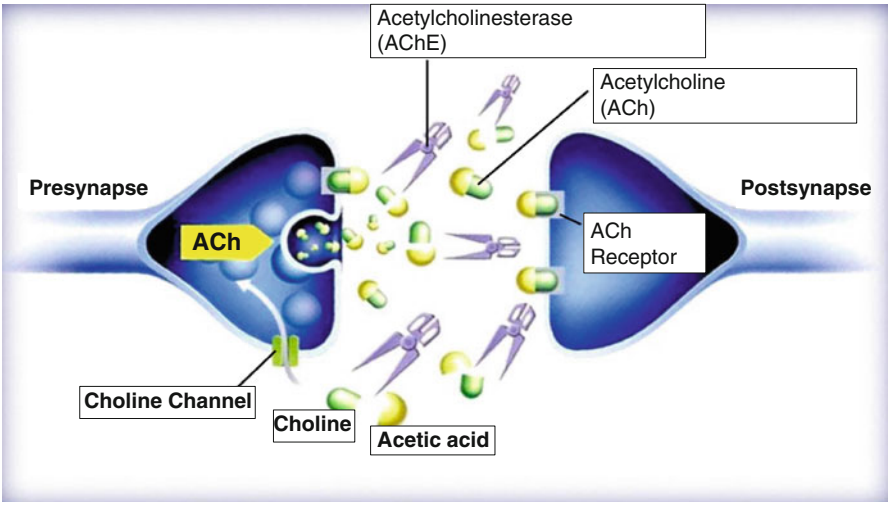

Fig. 2.1 Neurotransmission of cholinergic synapse. In the synaptic cleft of cholinergic neuron, acetylcholine (ACh) is decomposed into choline and acetic acid by acetylcholinesterase (AChE)

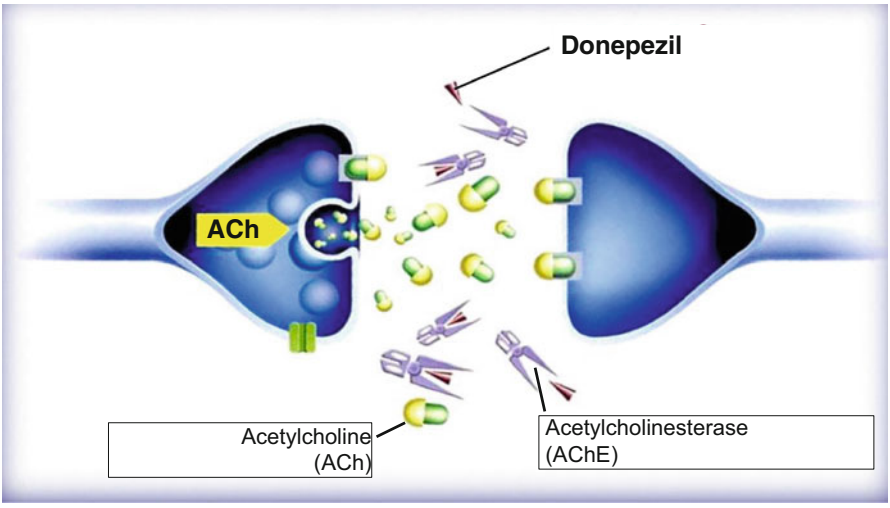

Fig. 2.2 Donepezil impedes AChE resulting in an increase of Ach level in the synaptic cleft

2.1.1 ACh and Donepezil

According to the ACh hypothesis, a reduction in brain ACh levels is thought to be the cause of AD. AChE is an enzyme that breaks down ACh and makes it inactive. Donepezil impedes AChE and prevents the breakdown of ACh. This elevates the concentration of free ACh in the synaptic cleft, thereby activating cholinergic nerves and stopping the progression of cognitive failure mechanisms in AD patients (Fig. 2.2).

Butyrylcholinesterase (BuChE) is another in vivo cholinesterase. Whereas AChE is present mainly in neurons, BuChE is found in peripheral nerves and glia. It has low substrate specificity, and little is known about its physiological functions. Donepezil has an approximately 122-fold higher inhibitory effect on AChE than BuChE, as well as a high selectivity for AChE (Darvesh et al. 2003). To examine the selectivity of donepezil for central and peripheral nerves, researchers studied the minimum effective amount needed to elevate cerebral cortex ACh. They also studied the minimum effective amount to induce fasciculations, a peripheral nerve effect. The results showed that donepezil has a strong selectivity for cholinergic nerves (Kosasa et al. 1999). These facts likely explain why donepezil causes few peripheral adverse reactions. Donepezil has a long blood half-life, between 70 and 80 h, and can be administered once daily.

2.2 Effects Against AD

2.2.1 Effects on Cardinal Symptoms in Mild to Moderate AD

Donepezil was administered at 5 mg/day for 24 weeks to mild and moderate AD patients, and the ADAS-cog was used to evaluate cognitive function over time. Although almost no changes were seen in the placebo group, the ADAS-cog final score in the donepezil group dropped by 2.80 points, demonstrating an improvement in cognitive function (Homma et al. 2000).

A meta-analysis of donepezil randomized clinical studies conducted between 1986 and 2006 targeting dementia patients showed a significant improvement of cognitive function in AD patients (Raina et al. 2008).

The efficacy of long-term donepezil administration was also studied in mild and moderate AD patients. The results showed donepezil prevented a reduction in cognitive function for approximately 5 years (Roger et al. 2000).

2.2.2 Effects on Cardinal Symptoms in Advanced AD

Donepezil was administered at 5 or 10 mg/day to advanced AD patients (FAST stage: 6+; Mini-Mental State Examination (MMSE): 1–12 points). Those given 10 mg saw a significant improvement in the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) and Severe Impairment Battery (SIB) scores (Homma et al. 2008).

2.2.3 Effects on the Biological and Psychological Symptoms of Dementia (BPSD) and on Caretaker Burden

The effects of donepezil on BPSD in mild and moderate AD patients were investigated using Neuropsychiatric Inventory (NPI) scores. The results showed

improvement in BPSD (Holmes et al. 2004). A meta-analysis also revealed cholinesterase inhibitors, including donepezil, and showed improvement effects against BPSD (Trinh et al. 2003).

BPSD places a serious burden on caretakers. In one study, the time spent actually caring for a patient in his or her home was measured for a period of 1 year. The donepezil group saw nursing care time reduce by an hour each day, compared to the placebo group (Wimo et al. 2004). This result appears to be donepezil's effect on BPSD.

2.2.4 Effects on Slowing Disease Progression

AD patients whose MMSE scores were ~20 prior to the release of donepezil saw their scores decrease by an average of approximately three points a year. Patients given donepezil showed a temporary increase in MMSE scores, followed by a decrease. However, the decrease was less than one point a year (Tomita et al. 2007).

Administration of donepezil was also shown to prolong the period patients could maintain ADL function by 72 %b (Mohs et al. 2001). This is reflected in data showing that those who took donepezil were able to delay placement in a nursing home by approximately 22 months compared to patients who did not take donepezil (Geldmacher et al. 2003).

As seen, donepezil is expected to affect disease progression. What sort of mechanism is at play? Neurotoxicity induced by glutamic acid administration is markedly suppressed by donepezil administered 24 h in advance, thus it appears to have neuroprotective effects (Takada et al. 2003). This suggests that donepezil is involved with nicotine receptors, in addition to its cholinesterase inhibition effects. Because it was reported that nicotine prevents glutamate neurotoxicity through nicotinic receptors (Akaike et al. 2010), donepezil was administered to mild and moderate AD patients for 24 weeks, and changes in hippocampal volume were measured before and after administration. The results revealed a significant difference between the two groups. Although a volume decrease was observed in the placebo group, no volume change was observed in the donepezil group (Krishman et al. 2003). There is data showing donepezil promoted neurogenesis in the hippocampus, to explain this effect (Kotani et al. 2006). Furthermore, although intraventricular injection of β-amyloid peptide (Aβ25–35) brings about lipoperoxidation, indicating hippocampal neurotoxicity, it is attenuated by donepezil administration (Meunier et al. 2006).

2.3 Effects Against Vascular Dementia

A double-blinded study in Europe and the USA reported efficacy against vascular dementia (VaD) (Roman et al. 2005). However, since it could not be ruled out that AD patients may have been included in the subject population, health insurance companies do not cover the use of donepezil for VaD (Maruki 2010). However, donepezil is recognized to be effective for the AD-VaD mixed type; therefore, health insurance companies cover its use in these patients (Rockwood et al. 2013).

2.4 Effects Against Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is a disease characterized by Parkinsonism and dementia. However, many Parkinson's disease (PD) patients present with both motor symptoms and cognitive dysfunction that progress slowly. Thus, DLB is also called PD dementia (PDD). Until now, PDD and DLB were differentiated according to the order in which Parkinsonism and dementia develop. However, since both diseases have Lewy bodies as a pathologic common finding, we will handle both DLB and PDD (which includes PD) in this chapter by referring to them collectively as Lewy body disease.

2.4.1 Intracerebral ACh Nerves

ACh nerves, which are central nerves, can be broadly classified into three systems. ACh-ergic interneurons are present inside the striate body. These interneurons are in close contact with dopaminergic (DA-ergic) neuron endings, regulating the DA-ACh balance (Aosaki et al. 2010). In PD, DA neuron endings projecting from the substantia nigra pars compacta are progressively lost. Because of this, ACh becomes predominant inside the striatum, relatively speaking, and disrupts the DA-ACh balance. Anticholinergic drugs are effective against PD motor symptoms, including tremor.

Two other ACh-ergic neuron systems project onto the entire central nervous system over an extremely broad range. However, they do not directly contact DA systems. One is a system projecting onto the cerebral neocortex as a whole from the basal forebrain, including the nucleus basalis of Meynert, and limbic system (such as the amygdala and hippocampus) (Selden et al. 1998). Another is a system projecting from the dorsolateral pontine tegmentum, including the pedunculopontine nucleus, to the thalamus, basal ganglia, hypothalamus, medullary reticular network, and the spinal cord (Lee et al. 2000). In DLB, the function of these central nervous system ACh nerves declines extensively, with the degree of dysfunction being even greater than seen with AD (Bohnen et al. 2003). Regarding the pedunculopontine nucleus–thalamus system, in DLB the functions of all ACh systems decline beginning in the early stages of disease (Muller and Bohnen 2013). Of special interest are reports noting that impediment of basal ganglia–cerebral cortex projections were related to a decline in cognitive function (Bohnen et al. 2009), that the pedunculopontine nucleus–thalamus system was related to gait disturbances and falls (Bohnen et al. 2012), and that the degree of functional decline was related to a decline in gait speed (Bohnen et al. 2013).

2.4.2 Donepezil Effects Against DLB

Because of the extensive ACh nervous system dysfunctions seen in Lewy body disease, hopes were pinned on donepezil effects in DLB. A randomized controlled trial was performed in which donepezil was administered to DLB subjects for 12 weeks. The donepezil subjects given 5 or 10 mg per day showed significantly fewer

abnormal behaviors and improved cognitive function. The government therefore approved an expansion of donepezil indications to include DLB (Mori et al. 2012).

As mentioned previously, however, striatal ACh and DA are held in a balanced relationship. Therefore, activation of ACh carries the risk of aggravating parkinsonian symptoms. In fact, one report shows donepezil can aggravate Parkinsonism and DLB symptoms, such as irascibility. However, clinical research has thus far not shown donepezil to significantly aggravate motor symptoms (Ikeda et al. 2013).

2.5 Clinical Use

Donepezil was the first anti-dementia drug to be approved. As a result, a considerable amount of evidence, safety data, and usage experiences have accumulated. Rapidly disintegrating oral tablets and oral jelly tablets are also being marketed, making it convenient for patients to choose a dosage form suiting their needs.

It has been reported that moderate to advanced AD patients given 23 mg/day of donepezil obtained better results than those given 10 mg/day. Because of donepezil's high tolerability, administration of 23 mg/day gained US approval in 2010.

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Galantamine for Alzheimer's Disease and Alzheimer's Disease with Cerebrovascular Disease

3

Kenneth L. Davis

3.1 Introduction

Despite numerous attempts to develop new classes of compounds for either the progression or symptomatic treatment of Alzheimer's disease, there have been no successes to date. Hence, the mainstay of the treatment of mild-to-moderate Alzheimer's disease (AD) remains the cholinesterase inhibitors. Despite the widespread use of these drugs, there is scant literature discussing the relative differences among these compounds and the practical consequences of those differences. Indeed, a recent review in a respected journal notes that "AD … responds only marginally and briefly to currently available drugs" (Bloom 2014). The purpose of this review article is to delineate the important properties that distinguish these compounds and the clinical implications of those differences. It will do so by largely focusing on donepezil, the most frequently prescribed cholinesterase inhibitor, and contrasting donepezil with galantamine, the cholinesterase inhibitor that differs the most in its mechanism of action within this class of compounds.

Two key properties differentiate donepezil and galantamine. These properties are the drugs' interaction with nicotinic receptors and their half-lives. Galantamine has been shown to be a positive allosteric modulator of nicotinic receptors, a property not shared by donepezil (Samochocki et al. 2003). Galantamine has a half-life of 7–8 h (Product Monograph 2008). In contrast, donepezil's half-life in the elderly is approximately 104 h (Ohnishi et al. 1993). The consequences of continuous, as compared to physiologically timed cholinesterase inhibition, will be addressed below.

3.2 Nicotinic Enhancement

Galantamine's enhancement of nicotinic receptors is especially pronounced at the $\alpha_4\beta_2\alpha_5$ receptor (Kuryatov et al. 2008). Galantamine potentiates depolarization of $\alpha_4\beta_2$ nicotinic receptors in human embryonic kidney-263 cells (Samochocki et al. 2003). That effect is blocked by FK-1, an antibody that specifically binds the

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Table 3.1 Incidence of diarrhea in controlled clinical trials of cholinesterase inhibitors cited in 2002 Physicians' Desk Reference (PDR)

Drug (dose)	PDR page #	Total *n*		% with diarrhea		% drug–% placebo (%)
		Drug	Placebo	Drug (%)	Placebo (%)	
Tacrine (40–160 mg)	1354	634	342	16	5	11
Galantamine (16–24 mg)	1796	1040	801	9	7	2
Rivastigmine (6–12 mg)	2344	1189	868	19	11	8
Donepezil (5–10 mg)[a]	2666	747	355	10	5	5

[a]3 % discontinuation rate for diarrhea in patients taking 10 mg/day (page 2666)

galantamine positive allosteric modulatory site on nicotinic receptors. Galantamine has a similar effect on α_7 receptors in xenopus oocytes (Texido et al. 2005). Donepezil does not enhance the activity of nicotinic receptors beyond the effect of acetylcholinesterase inhibition. This difference suggests that galantamine should have a profile with more nicotinic activity than does donepezil. Conversely, donepezil should have a profile that favors more muscarinic activity than does galantamine. These differences, in nicotinic stimulation, and those in duration of action, to be discussed later, have profound clinical implications that are just being recognized.

3.2.1 Peripheral Cholinergic Effects

One simple way to differentiate nicotinic and muscarinic clinical effects is the relative incidence of diarrhea, as diarrhea is a reflection of muscarinic activity. The large, double-blind, placebo-controlled registration studies reported in the Physician's Desk Reference indicate that the relative difference in the incidence of diarrhea between patients on rivastigmine or donepezil compared to placebo is large. Donepezil patients reported diarrhea 100 % more frequently than placebo patients (Medical Economics Staff 2002). In contrast, galantamine patients had only 29 % more diarrhea than their placebo counterparts. Table 3.1 summarizes these differences.

3.2.2 Cognitive Profile

The cognitive profiles of galantamine and donepezil demonstrate a difference that can be attributed to enhanced nicotinic stimulation by galantamine. A 52-week, rater-blinded study directly compared the effects of donepezil and galantamine on the Mini-Mental State Exam (MMSE) and the Alzheimer's Disease Assessment Scale—cognitive (ADAS-cog) (Wilcock et al. 2003). In a preplanned analysis of patients meeting the UK's National Institute of Clinical Excellence criteria for moderate AD (having MMSE scores from 10 to 18), the two drugs significantly differed in their ability to improve performance on the attention and language subscales over

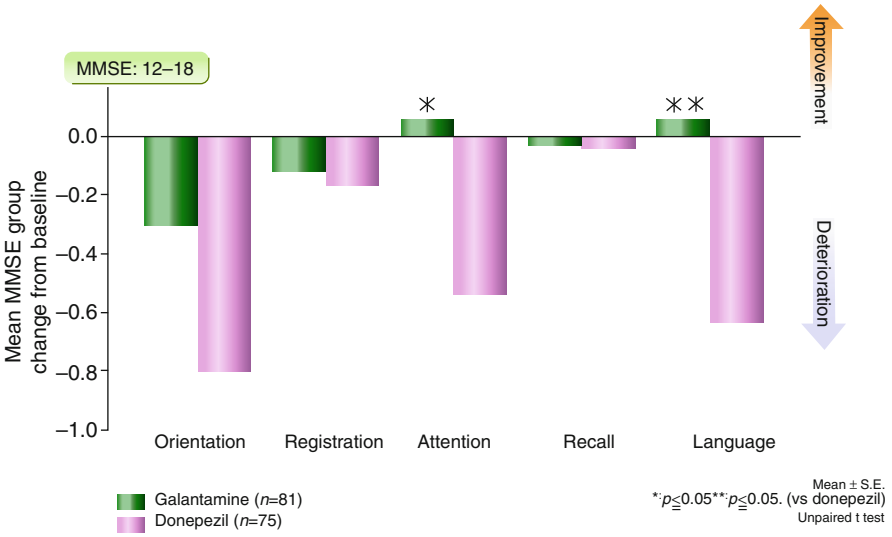

Fig. 3.1 Galantamine patients scored significantly better than donepezil patients on MMSE (Mini-Mental State Exam) subscales requiring attention and working memory, both of which involve nicotinic mechanisms. The drugs were compared in a randomized, 1-year, rater-blinded study in patients with MMSE scores of 12–18. *MMSE* Mini-Mental State Exam (Wilcock et al. 2003)

the 52 weeks of the study, as shown in Fig. 3.1. The language subscale contains commands, which require working memory. Both attention and working memory can be enhanced by nicotinic stimulation. On the ADAS-cog, performance on the "commands" question was also significantly better in galantamine than donepezil patients (data on file). This pattern of results with galantamine is consistent with its ability to enhance central nicotinic activity beyond cholinesterase inhibition, through allosteric modulation of receptors.

3.2.3 Neuroprotection

As the experimental therapeutics of AD has evolved, increased emphasis has been placed on the development of compounds that would offer neuroprotection, enhance the clearance of β-amyloid (Aβ), or decrease the formation or toxicity of various forms of the Aβ peptides. Nicotinic activity can mediate both neuronal survival and Aβ clearance. That nicotinic mechanisms may be neuroprotective has strong epidemiologic support in a preventive effect of smoking on the incidence of Parkinson's disease. There is a beneficial effect of duration of smoking, and neuroprotection has been demonstrated in identical twins discordant for smoking (Chen et al. 2010). While lifestyle and many other physiological effects of smoking may contribute to these findings, the $\alpha_4\beta_2$ and a_7 nicotinic receptors can mediate neuroprotective mechanisms (Kawamata and Shimohama 2011). Smoking itself does not lower the incidence of AD, perhaps due to adverse effects on other organ systems (Kulkull 2001).

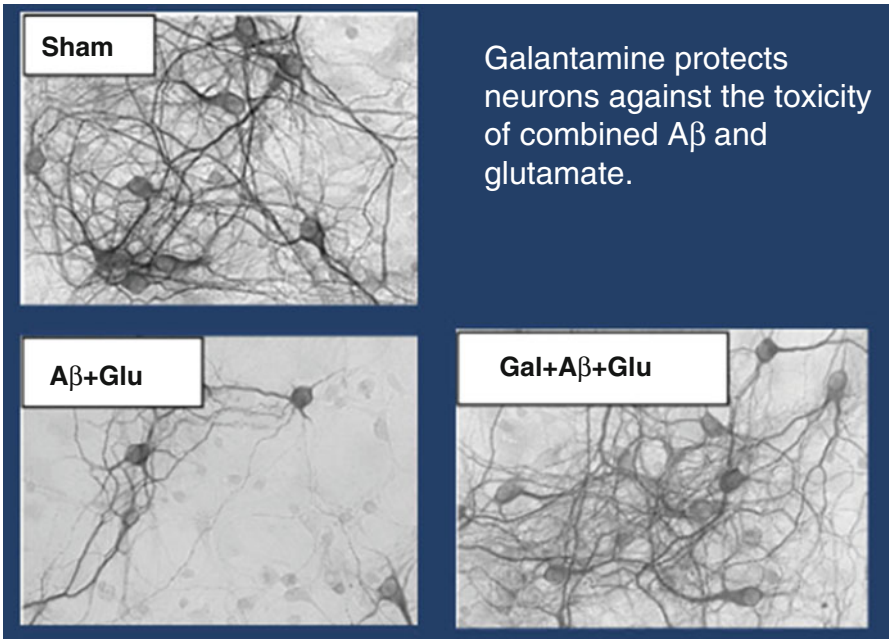

Fig. 3.2 Galantamine exerts a protective effect against β-amyloid (Aβ)-enhanced glutamate cytotoxicity. Aβ, $A\beta_{1-40}$ (10.0 nM) + $A\beta_{1-42}$ (1.0 nM) 4 days; Glu, glutamate (20.0 μM) 24 h; Aβ + Glu, 4-day treatment with Aβ followed by 24-h treatment with glutamate; Gal, simultaneous treatment with galantamine and Aβ for 4 days (1.0 and 10.0 μM). Galantamine 1.0 and 10.0 μM significantly protected neurons against Aβ-enhanced glutamate neurotoxicity ($p < .01$) (Kihara et al. 2004)

Depending on brain region, 11–37 % of $\alpha_4\beta_2$ nicotinic receptors have as their fifth member, the α_5 subunit (Kuryatov et al. 2008). These $\alpha_4\beta_2\alpha_5$ subtypes are more sensitive to agonists and produce a larger maximal current than $\alpha_4\beta_2$ receptors lacking the α_5 subunit (Mao et al. 2008). Galantamine, at clinical concentrations, enhances the activity of $\alpha_4\beta_2\alpha_5$ receptors by 220 %, as compared to 20–30 % for other nicotinic receptors (Kuryatov et al. 2008). As shown in Fig. 3.2, galantamine, applied simultaneously with a combination of glutamate and Aβ species, blocks their neurotoxic effect (Kihara et al. 2004). In a separate experiment, 24-hour pretreatment of a neuronal culture with galantamine increased survival following a toxic dose of glutamate by 78 % ($p < .01$). The protection against glutamate was nicotinic, as mecamylamine blocked 2/3 of galantamine's benefit. Dihydrobetaerythroidine, an $\alpha_4\beta_2$-blocker, reduced the galantamine effect by a little more than half, while methyllyaconitine, an α_7-antagonist, caused a 1/3 reduction (all $p < .01$) (Takada-Takatori et al. 2006). Thus, galantamine's potent effect on an especially active subset of $\alpha_4\beta_2$ receptors may play a large part in galantamine-induced neuroprotection. Cholinesterase inhibitors which do not enhance nicotinic receptor function through allosteric enhancement may nevertheless be expected to have some nicotinic activity. Thus, donepezil can protect neurons against glutamate toxicity, but is 10× less potent than galantamine (Takada-Takatori et al. 2009).

3.2.4 Aβ Clearance

Nicotinic stimulation can also enhance Aβ clearance. This becomes particularly relevant in light of studies that indicate that the key abnormality in Alzheimer's disease of late-onset (LOAD) is the inability to adequately clear Aβ. When Aβ clearance was measured following the infusion of labelled leucine and cerebrospinal fluid (CSF) was sampled hourly, patients with LOAD were 30 % less efficient at clearing Aβ than controls (Mawuenyega et al. 2010). This finding took on increasing importance following a large study of brains from LOAD patients and controls. Bayesian analysis of the gene expression that differentiated these two groups indicated that upregulation of genes in the immune/microglial module in LOAD patients best differentiated them from controls. Gene expression in the immune/microglial module was most highly correlated with neuropathology traits such as frontal and parietal atrophy and ventricular enlargement. The authors note that alleles of genes found in genome-wide association studies to increase the risk of LOAD, such as CD33 and TREM2, also fall within the immune/microglial network. To further explore this finding, the central gene in the network, TYROBP, was overexpressed in microglial cells. This resulted in downregulation of 99 % of functional genes within the microglia, such as those involved in RNA metabolism and cell-cycle mitosis (Zhang et al. 2013). Microglia perform many functions which can variously exacerbate or attenuate the Alzheimer process. Microglial function may be impaired in LOAD patients.

The importance of the elucidation of a group of genes that influences immune modulation and microglial activity that differentiates LOAD patients from controls was underscored in an editorial discussing an experiment in which CD33, a microglial-surface protein increased in LOAD, inhibited Aβ clearance (Gandy and Heppner 2013). The editorial pointed out that microglia can exist in an inflammatory, harmful state, or an amyloid-clearing, helpful state and that "microglia-targeted therapies must be finely targeted." It noted that there were only two approved drugs that were known to increase the phagocytic activity of microglia, the PPARγ agonist pioglitazone and the mixed acetylcholinesterase inhibitor–nicotinic allosteric agonist galantamine (Takata et al. 2010). This property is illustrated in Fig. 3.3 which demonstrates galantamine's ability to promote Aβ clearance by interacting with its allosteric nicotinic modulatory site on microglia. The enhancement of Aβ clearance can be completely blocked by the antibody FK-1 which blocks the galantamine modulatory site on nicotinic receptors.

Amyloid deposits in the brains of APdE9 mice carrying amyloid precursor protein (APP) and presenilin 1 (PS1) mutations, control and galantamine treated, are shown in Fig. 3.4. The brain slice shown in the left panel was from a mouse treated with galantamine, 5 mg/kg/day for two months prior to sacrifice at 11 months, resulting in a significant reduction in amyloid deposits. Additionally, treated mice showed improved learning and spatial memory in the water maze test (Takata et al. 2010). A similar result has been reported for short-term donepezil treatment of APP/PS1 mice (Easton et al. 2013). A 10-day treatment of Tg2576 (APPswe) mice with galantamine increased synaptophysin levels, but did not reduce Aβ species (Unger et al. 2006). These data indicate that cholinesterase inhibitors may be able to influence amyloid deposition in animal models of familial Alzheimer's disease.

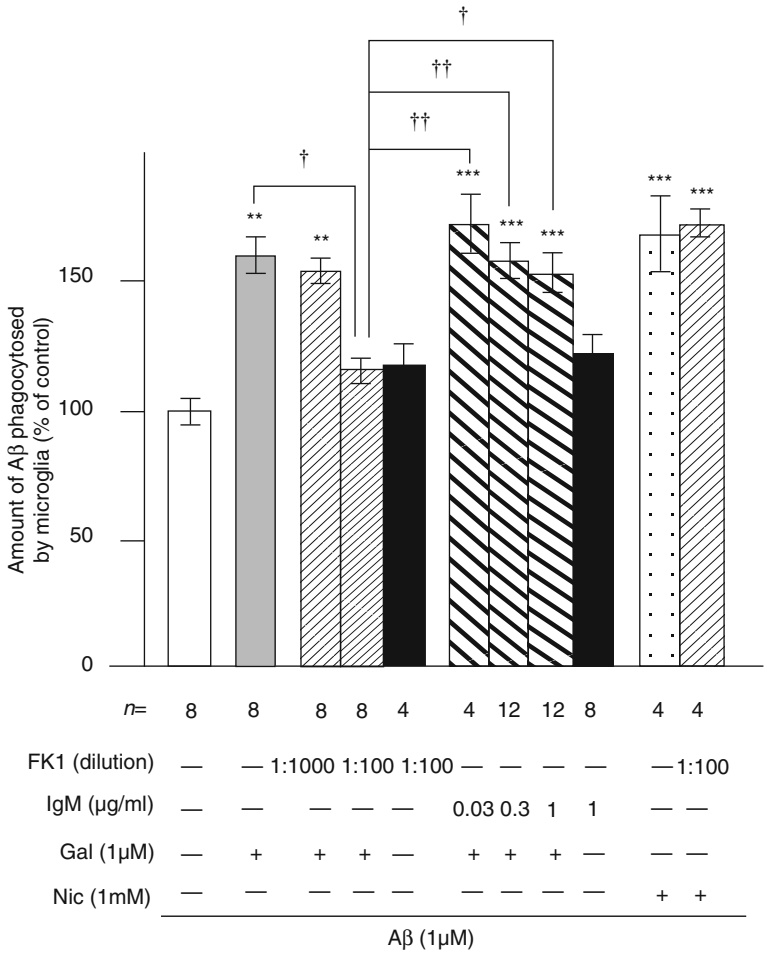

Fig. 3.3 Involvement of the APL-binding site for nAChRs in galantamine-enhanced microglial Aβ phagocytosis. Rat microglia were treated with 1 μM Aβ42 in the presence or absence of 1 μM galantamine or 1 mM nicotine. FK1 antibody or mouse IgM isotype control was added 10 min before treatment with Aβ42. The amounts of Aβ phagocytosed by microglia were measured by ELISA. **, $p < .01$; ***$p < .001$; versus Aβ42 alone. †, $p < 0.05$; ††, $p < 0.01$ versus Aβ42 plus galantamine and FK1 antibody (1:100). *FK1* FK1 antibody, *IgM* mouse IgM isotype control, *Gal* galantamine, *Nic* nicotine, *n* number of samples (Takata et al. 2010)

3.3 Human Clinical Data

3.3.1 Biomarkers

Changes in amyloid dynamics under the influence of galantamine have been shown in humans as well. CSF Aβ was measured in a 3-month head-to-head study of galantamine, donepezil, and rivastigmine in mild-to-moderate AD patients (Nordberg

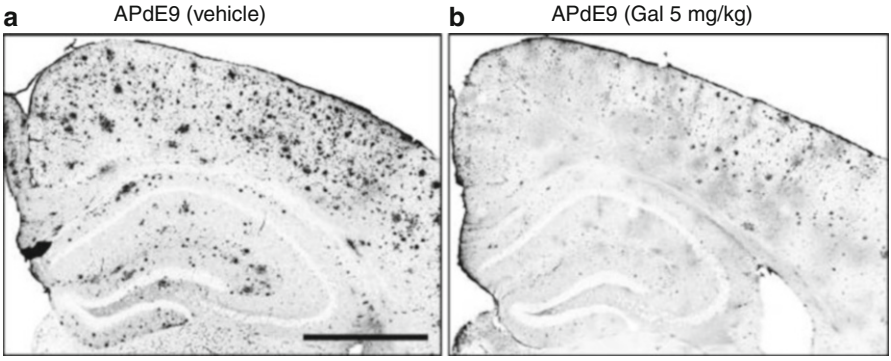

Fig. 3.4 Galantamine increased Aβ clearance in the brains of APdE9 mice. *A* and *B*, brain sections of vehicle-treated (**a**) or galantamine-treated (**b**) APdE9 mice were immunostained with anti-Aβ antibody. Mice were treated with 5 mg/kg daily of galantamine, or vehicle, for 2 months and sacrificed at 11 months. *Scale bar,* 500 μm (Takata et al. 2010)

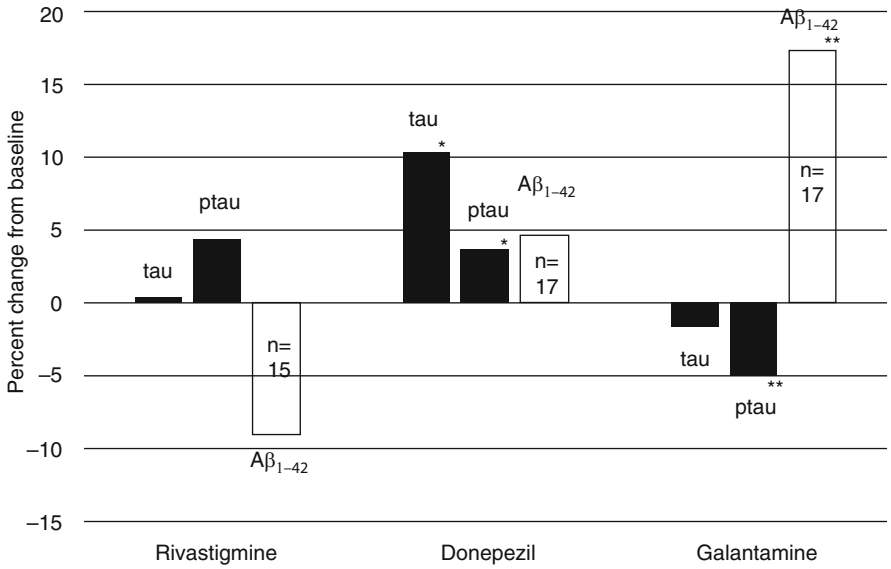

Fig. 3.5 Percent changes in CSF tau, ptau and $A\beta_{1-42}$ in patients completing 13 weeks of treatment with galantamine, donepezil, or rivastigmine; $*p<0.05$ *versus* baseline at 13 weeks, using one-way t-test; $**p<0.05$ *versus* rivastigmine, using an ANOVA model with treatment as the factor and baseline value as the covariate. *CSF* cerebrospinal fluid, *ptau* phosphotau (Data from Nordberg et al. 2009)

et al. 2009). Patients were randomized to each of the three drugs, and CSF was collected at baseline and endpoint and analyzed by personnel blinded to treatment and sample order. CSF $A\beta_{1-42}$ rose 17 % in galantamine patients, which was significantly different from the outcome in rivastigmine patients (Fig. 3.5). Figure 3.6 shows the CSF biomarker changes following treatment with the cholinesterase inhibitors in the

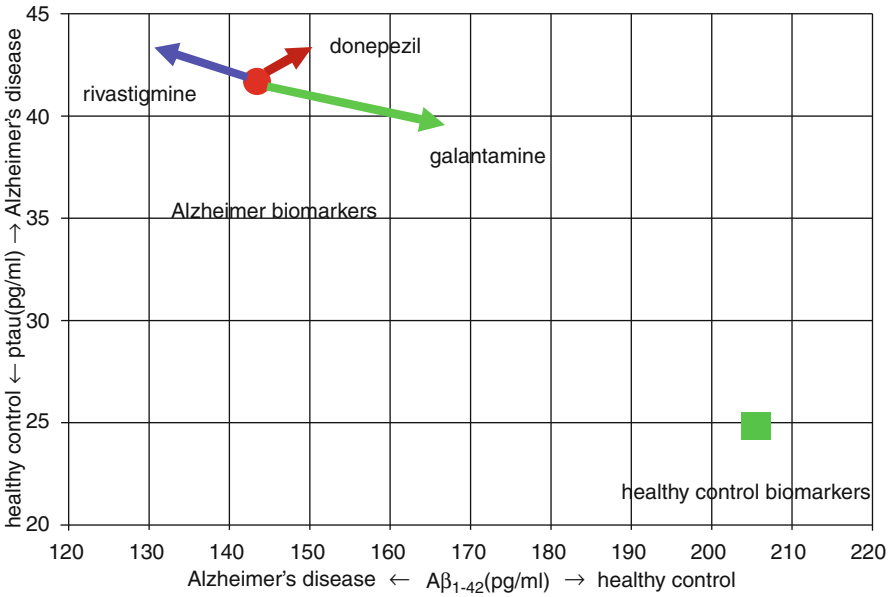

Fig. 3.6 Changes in CSF $A\beta_{1–42}$ and ptau following three months of rivastigmine, donepezil, or galantamine treatment of AD patients are shown in relation to average values for AD (*circle*) and healthy controls (*square*) from the ADNI database. Percentage changes from Nordberg et al. were applied to the ADNI baseline values. Significant differences in rivastigmine and galantamine effects on CSF $A\beta_{1–42}$ and ptau are apparent, as rivastigmine moves biomarkers away from healthy control values, while galantamine moves biomarkers towards those of control subjects (Data from Nordberg et al. (2009) and Okonkwo et al. (2010))

context of typical healthy control and Alzheimer values from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The percentage changes in baseline CSF $A\beta_{1–42}$ and phosphotau (ptau) which were reported by Nordberg et al. were applied to the mean CSF $A\beta_{1–42}$ and ptau values for AD patients from the ADNI database (Okonkwo et al. 2010). The statistically significant differences between rivastigmine and galantamine in CSF $A\beta_{1–42}$ and ptau are easily appreciated in Fig. 3.6, with rivastigmine moving biomarker values away from and galantamine moving $A\beta_{1–42}$ and ptau towards healthy control values. Numerous compounds have cleared amyloid from various mouse animal models and have not altered the progression of the Alzheimer process. Biomarkers of Alzheimer's disease still need further validation. The litmus test for whether any of these results has practical significance rests on clinical studies either in patients with AD or mild cognitive impairment (MCI). Since the average AD patient lives 8 years from the time of diagnosis, the most useful clinical studies are not the 6-month trials that have been used for registration purposes, rather they are trials of several years' duration. Three placebo-controlled, randomized studies have been carried out in patients with MCI that report the effect of acetylcholinesterase inhibitors on the MRI biomarker, global brain atrophy. Over the course of 29 months, global atrophy was not significantly diminished in

patients receiving donepezil compared to controls, nor was it at any time point in a four-year rivastigmine study (Jack et al. 2008; Feldman et al. 2007). In contrast, over 24 months MCI patients receiving galantamine had significantly less global atrophy than controls (Scheltens et al. 2004). It should be pointed out however that galantamine is not approved or recommended for patients with MCI (Winblad et al. 2008).

3.3.2 Mortality

Thus, the data from the 2-year MCI trial of galantamine combined with the biomarker data support the notion that galantamine has properties that are not shared with other cholinesterase inhibitors, that this effect is likely mediated by the stimulation of allosteric nicotinic receptors, and that it could involve neuroprotection and/or amyloid clearance. However, by far the most compelling data differentiating galantamine from the other compounds in this class comes from a recently concluded two-year, placebo-controlled, randomized trial of galantamine in AD patients (Hager et al. 2014). This study entered 2045 patients with AD or AD with cerebrovascular disease. Thirty-five percent of these patients were male, their average age was 73, and their average MMSE score was 19. The demographic and baseline characteristics of the placebo and galantamine groups were similar.

Before this study could be completed the Data Safety Monitoring Board halted the investigation because they had observed excess deaths in one arm of the study. Upon analysis it was determined that patients receiving placebo had a significantly higher mortality than patients receiving galantamine. Specifically, 56 deaths occurred in patients receiving placebo which was 5.5 % of that cohort. In contrast, there were 33 deaths in patients receiving galantamine, or 3.2 % of that cohort. The hazard ratio was .58, statistically significantly favoring galantamine ($p = .01$). The results are displayed in Fig. 3.7. The mortality benefit appears to increase with time.

Other large, double-blind, placebo-controlled studies of cholinesterase inhibitor administration to patients with mild-to-moderate Alzheimer's dementia which have been conducted for varying periods have reported mortality. Those studies have been collapsed by duration of treatment and are presented in Table 3.2 (Rogers et al. 1998a, b; Burns et al. 1999; Tariot et al. 2000, 2001; Winblad et al. 2001; Mohs et al. 2001; AD 2000 Collaborative Group 2000; Raskind et al. 2000; Rockwood et al. 2001; Erkinjuntti et al. 2002; Brodaty et al. 2005; Homma et al. 2011; Hager et al. 2014). The data indicate that for a duration of drug administration of 6 months or less, there is a numerical diminution in mortality for patients taking either donepezil or galantamine compared to placebo. However, by 1 year, the advantage of donepezil on mortality is lost, and, by 2 years, the death rate in patients randomized to donepezil is 27–31 % higher than those randomized to placebo or to rivastigmine (Bullock et al. 2005). In contrast, the relative death rate on galantamine as compared to placebo at 6 months is maintained at 2 years.

Mortality in severe and vascular dementias has been assessed in a number of 3–6-month studies. In three vascular dementia studies, 5–10 mg donepezil was administered to 1475 donepezil patients and 718 placebo patients. The mortality

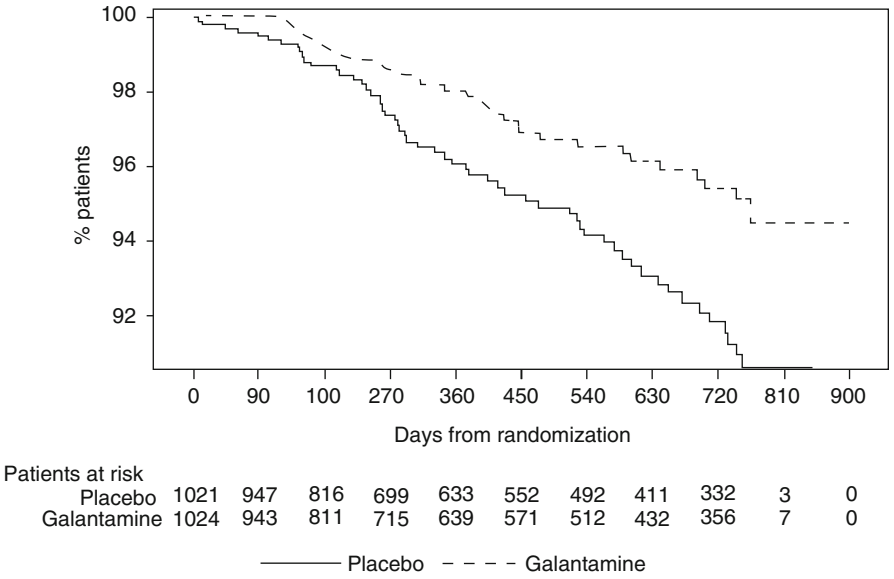

Fig. 3.7 Time from randomization to death (safety analysis set) (Hager et al. 2014)

Table 3.2 Mortality over time in double-blind, placebo-controlled, randomized trials in mild-to-moderate Alzheimer's dementia

	Donepezil			Galantamine		
	Donepezil deaths/*n*	Placebo deaths/*n*	Hazard ratio	Galantamine deaths/*n*	Placebo deaths/*n*	Hazard ratio
3–6 months	7/1274	11/693		24/2803	16/1334	
%	.55 %	1.59 %	0.35	.86 %	1.20 %	0.71
1 year	7/356	7/361				
%	1.97 %	1.94 %	1.01			
2 years	63/242	50/244		33/1024	56/1021	
%	26.0 %	20.5 %	1.27	3.22 %	5.49 %	0.59

rates were 1.6 % for drug, and 1.1 % for placebo, a ratio of 1.46 (Black et al. 2003; Wilkinson et al. 2003; Roman et al. 2010). In contrast, the mortality ratio during a galantamine vascular dementia study was 0.49, as 5/396 (1.3 %) of galantamine patients and 10/390 (2.6 %) of placebo patients died (Auchus et al. 2007). In moderate-to-severe AD dementia studies, deaths totalled 28/773 (3.6 %) in donepezil patients and 32/669 (4.8 %) in placebo patients, a ratio of 0.76 (Black et al. 2007; Homma et al. 2008; Feldman et al. 2001; Winblad et al. 2006; Howard et al. 2007). Galantamine significantly reduced mortality in its one study in severe dementia. Death occurred in 8/207 (3.9 %) galantamine and 21/200 (10.5 %) placebo patients, a ratio of 0.37 (Burns et al. 2009). Thus, short-term mortality in galantamine-treated

Table 3.3 Serious treatment-emergent adverse events[a] ≥2 %, hospitalizations, and deaths

	% incidence		% hospitalized		% death	
	pla	gal	pla	gal	pla	gal
Study totals	**12.0**	**12.6**	**8.6**	**11.0**	**4.6**	**3.0**
Nervous system (e.g., AD, stroke)	4.1	2.8	3.2	2.2	1.1	0.7
Cardiac (e.g., failure, myocardial infarction)	2.4	2.2	0.8	1.2	1.8	1.3
Infections, infestations (e.g., pneumonia)	1.5	2.0	0.6	1.7	0.5	0.4
Injury, poisoning, procedural complications	2.2	2.0	1.8	2.0	0.2	0.1

pla placebo, *gal* galantamine (data on file)

[a]Note these are fewer than all deaths, as the events preceding 11 deaths occurred >30 days from drug administration and thus were not treatment emergent

patients with dementias appeared to be favorably affected, which does not seem to be the case for donepezil use in vascular dementia.

In contrast to galantamine's favorable results in dementia populations, a 2-year study of 16–24 mg galantamine and a 3-year study of 10 mg donepezil in MCI patients showed drug/placebo mortality ratios greater than unity. The mortality ratio for galantamine at 2 years was 1.7 (34/1026, 3.3 %, of galantamine, and 20/1022, 2.0 %, of placebo patients) (Winblad et al. 2008). The risk appeared to be nominally greatest earlier in the study, as shown in Figure 5 of Winblad et al. 2008. In the 3-year donepezil study, 7/259 (2.7 %) of donepezil, 5/253 (2.0 %) of placebo, and 5/257 (1.9 %) of vitamin E patients died, a donepezil/placebo ratio of 1.35, similar to that of the 2-year donepezil trial in AD patients (Petersen et al. 2005). These drugs are not recommended for use in MCI.

Returning to the substantial mortality reduction in patients with mild-to-moderate AD, a 42 % decrease with galantamine at 2 years needs an explanation. Serious adverse events occurring during or within 30 days of treatment did not differ between galantamine (12.6 %) and placebo patients (12.0 %). The hospitalization rate for galantamine patients, however, was 11 %, as compared to 8.6 % for placebo patients. The largest categories of serious adverse events and their hospitalization and death rates are presented in Table 3.3. It is apparent that there was no diagnostic category containing at least 2 % of the treatment-related serious adverse events whose mortality was relatively more diminished than any other. However, patients on galantamine who had serious treatment-emergent symptoms, except for neurological symptoms including AD, were hospitalized more frequently, and died less frequently, than placebo patients. This raises the possibility that galantamine patients responded differently from placebo patients when a serious adverse event occurred. The cognitive and functional effects of galantamine therapy are presented below.

3.3.3 Cognitive and Functional Outcomes

The results of the MMSE over the course of this study are presented in Fig. 3.8. The last observation carried forward, intent-to-treat analysis shows a highly statistically

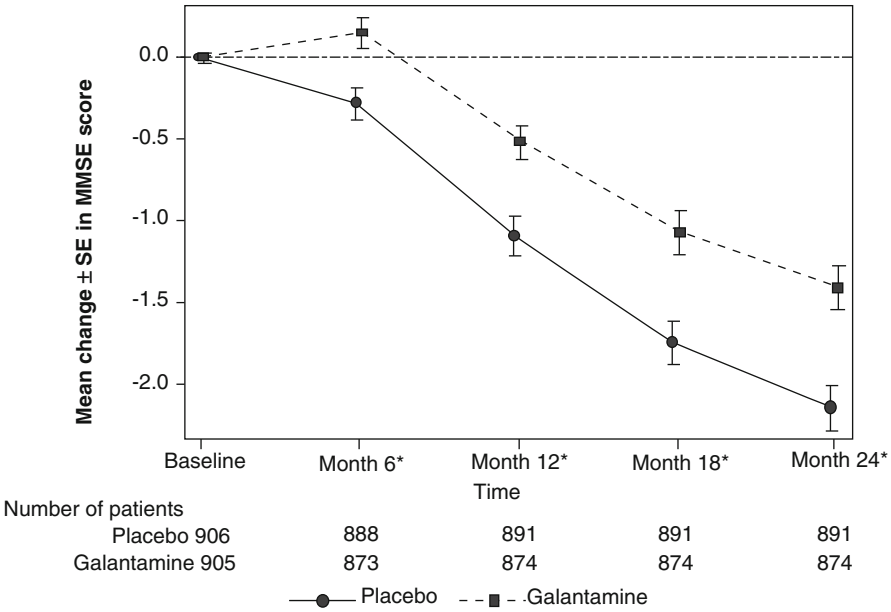

Fig. 3.8 Mean change in MMSE scores over time (LOCF) (ITT analysis set). *Significant difference between galantamine and placebo in MMSE score change from baseline. Estimates of treatment difference (95 % Cls) of MMSE using the repeated measures model (OC) were −0.48 (−0.73 to −0.22) at month 6, and −1.10 (−1.67 to −0.52) at month 24. *Cl* confidence interval, *ITT* intent-to-treat, *LOCF* last observation carried forward, *MMSE* Mini-Mental State Examination, *OC* observed case, *SE* standard error (Hager et al. 2014)

significant difference favoring galantamine over placebo at 6 and 24 months ($p < .001$). As measured by the Disability Assessment for Dementia (DAD), placebo patients took 17 months to reach the level of functional decline that galantamine patients experienced at 24 months. Mortality at 24 months in galantamine patients was at the level of placebo patients at 17 months as well. The MMSE and DAD subscales most affected by galantamine may offer insights into patients' abilities and behaviors. The MMSE domains, in intention-to-treat analysis, which most differentiated galantamine from placebo patients were orientation, attention, and language. (Attention and language are the same scales noted above to differ between galantamine and donepezil patients and to utilize nicotinic mechanisms.) In the language question, a patient must remember and follow a 3-stage command, read and execute "Close your eyes," and compose and write a sentence (Folstein et al. 1975). The DAD scales most significantly enhanced were basic and instrumental activities of daily living, initiation, effective performance, and planning and organization (data on file). The basic activities category includes eating, hygiene, and dressing, while telephoning, taking medications, and staying safely at home are instrumental activities (Gelinas and Gautier 1994). Initiation is the ability to decide or start an action appropriately. Effective performance is completing an action successfully. And planning and organization is essentially executive function—the ability to

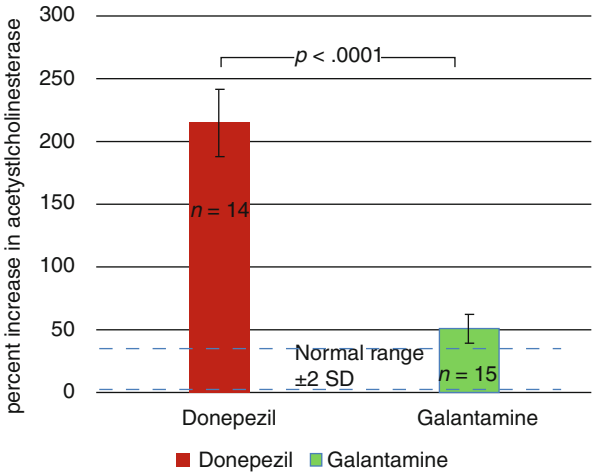

Fig. 3.9 Percent change in CSF acetylcholinesterase in patients completing 13 weeks of treatment with donepezil or galantamine. $p < 0.0001$, donepezil *versus* galantamine, using two-way *t*-test. *CSF* cerebrospinal fluid, *SD* standard deviation (Data from Nordberg et al. 2009)

structure an activity, obtain supplies, make decisions, and solve problems during its execution. One can begin to appreciate that this subset of skills, which is maintained to the greatest degree with galantamine therapy, might help a person maintain health and obtain and cooperate with help when it is needed. Thus, galantamine's ability to reduce cognitive and functional deterioration might have contributed to its mortality benefit.

3.3.4 Galantamine and Memantine

Some insight into a possible biological mechanism underlying the clinical results with galantamine is revealed by the subpopulation of patients who was receiving concomitant treatment with memantine along with either galantamine or placebo. An analysis of the MMSE scores at month 24 broken down by the concomitant use or nonuse of memantine reveals a surprising result as indicated in Fig. 3.9. Memantine use completely blocked galantamine's beneficial effect. It may simply be that memantine patients were sicker or unresponsive to cholinesterase inhibitors. Baseline MMSE values were significantly lower in memantine patients, by about a point. However, the decline of placebo-treated patients was similar whether or not memantine was taken. There is, however, a plausible pharmacological explanation. Memantine is an open-channel blocker of nicotinic receptors. Its distribution in the human brain is the same as that of the $\alpha_4\beta_2$-selective compound 5-[^{125}]-A-85380, being highest in the thalamus, followed by various cortical areas, with moderate binding in white matter (Ametamey et al. 2002; Pimlott et al. 2004). ^{18}F-memantine distribution did not correspond to that of TCP, an uncompetitive NMDA receptor blocker. Thus, memantine binding followed a nicotinic but not a glutamate-receptor pattern. Memantine blocks α_7 nicotinic receptors at an IC_{50} concentration of 5.1 μM and blocks $\alpha_4\beta_2$ nicotinic receptors at an IC_{50} of 7 μM (Aracava et al. 2005; Buisson

and Bertrand 1998). Memantine levels in plasma averaged 120 ng/ml during phase III studies in humans, about 0.67 μM (Periclou et al. 2006). Memantine partitions nearly 30× to brain tissue over plasma in rats (Saab and Roder 2011). Brain to plasma partitioning is similar in humans, as a 25:1 ratio was reached at the end of the PET study, at which time brain levels were still rising. All of these data taken together suggest that, in clinical use, memantine concentrations in brain tissue are well over 15 μM, blocking the nicotinic receptors whose function galantamine enhances. Thus, memantine negates galantamine's positive effect on the MMSE. This result would be consistent with an important role for nicotinic mechanisms in the cognitive effects of galantamine. The basic science therefore suggests that, in the clinic, galantamine may not have an effect in the presence of memantine, and this may be an inadvisable combination.

As previously noted, multi-year, double-blind, placebo-controlled studies of drugs approved for the treatment of AD are few, but highly relevant to the practicing clinician and to patients. The 2-year study of galantamine discussed above and the AD2000 collaborative study with donepezil are comparable studies that enrolled fairly similar populations, both including AD with or without concomitant cerebrovascular disease, used similar outcome measures, and included large numbers of patients, although AD2000 has been criticized for a high dropout rate. Thus, the outcomes of these studies offer some insight into the relative efficacy of these two drugs. In donepezil patients, functional and cognitive deterioration were each reduced by about 3 months over a 2-year period, compared to placebo. In contrast, galantamine reduced functional deterioration by 7 months, and cognitive deterioration by 9 months (11.4 months in patients not on memantine), in comparison to placebo.

Donepezil and rivastigmine have been compared in a large 2-year study (Bullock et al. 2005). Approximately 500 patients in each group contributed to the data analysis. This was a double-blind, randomized, controlled trial designed to evaluate the efficacy and tolerability of the two drugs, but did not contain a placebo control. There were no significant differences in cognitive or behavioral measures between the two drugs at the two-year time point.

3.3.5 Sleep Disturbance

Although the preclinical, cognitive, and mortality data outlined above might influence a clinician's decision on what drug to use in patients with AD, often those decisions are based on a drug's short-term adverse event profile. One side effect that is particularly problematic in patients with AD is insomnia. This problem is difficult for caregivers to cope with and, if severe, can lead to institutionalization as caregivers become exhausted. The incidence of insomnia for galantamine and donepezil across multiple pivotal studies is presented in Table 3.4 (Rogers et al. 1998a; Burns et al. 1999; Winblad et al. 2001; Mohs et al. 2001; Stahl et al. 2004). As can be seen from these comparisons, the incidence of insomnia in patients receiving galantamine over the initial period of

Table 3.4 Insomnia rates in pivotal clinical trials of donepezil and galantamine

Donepezil	Escalation to 10 mg/day (weeks)	Placebo		Donepezil 5 mg/day		Donepezil 10 mg/day	
		n	%	*n*	%	*n*	%
Rogers et al. (1998a)	1	153	5	157	8	158	18
Burns et al. (1999)	1	274	4	271	7	273	8
Winblad et al. (2001)	4	144	7	n/a	n/a	142	10
Mohs et al. (2001)	4	217	3	n/a	n/a	214	8

Galantamine	Escalation to 16–24 mg/day (weeks)	Placebo		Galantamine 8 mg b.i.d.		Galantamine 12 mg b.i.d.	
		n	%	*n*	%	*n*	%
Stahl et al. (2004)	2–8	714	2.2	279	1.1	705	2.6

treatment is markedly less than occurs with donepezil. Insomnia occurred in patients taking 5 mg donepezil at 1.6–1.8× the placebo rate, 2–3.6× more frequently in patients on 10 mg donepezil with a 1-week dose escalation, and 1.4–2.7× more frequently with a 4-week escalation. In contrast, insomnia in galantamine patients was half that in the placebo group at 16 mg and 1.2× the placebo rate at 24 mg. This was predictable, as normal brain acetylcholine levels fall markedly at night, and acetylcholinesterase activity rises, in order to permit sleep (Davis and Sadik 2006). Donepezil's multiple-day half-life greatly reduces the normal diurnal fluctuation of acetylcholinesterase activity (Tiseo et al. 1998). In response, acetylcholinesterase, as measured in CSF, increases dramatically in donepezil-treated patients, as will be discussed below.

Given the frequency of insomnia with donepezil treatment, it is not surprising that there is an increased use of hypnotics and other drugs that attempt to address this problem. Surveys of hypnotic administration in donepezil users as compared to nonusers show that the rate of hypnotic use among donepezil users was 2.65 times greater than in AD patients not taking donepezil (Stahl et al. 2003). In contrast, in patients participating in three double-blind clinical trials of galantamine, there was no significant difference in the use of sleep-promoting medications among placebo, 16 mg/day, and 24 mg/day patients, with percentages of 4.6, 2.9, and 5.6 %, respectively (Stahl et al. 2004). Thus, clinical observations are consistent with the basic science and confirm that donepezil interferes with sleep and is associated with hypnotic medication use.

Sleep disturbance in patients with AD is generally treated in one of two ways, with benzodiazepines and related compounds, or with neuroleptics. Both approaches are problematic. Hypnotics impair cognition, clearly a circumstance to be avoided in patients with AD, and neuroleptics impair cognition and are associated with increased mortality. Hence, the precipitation of sleep disturbance would seem an event to be avoided and would be a consideration when choosing among cholinesterase inhibitors.

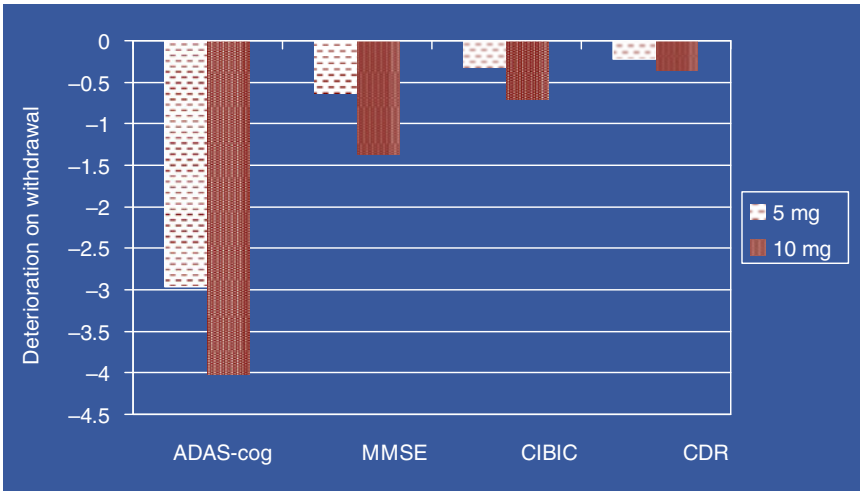

Fig. 3.10 A pattern of greater numerical decline in outcome measures is seen following 6 weeks of donepezil withdrawal from 10 mg as compared to 5 mg. *ADAS-cog* Alzheimer's Disease Assessment Scale—cognitive, *MMSE* Mini-Mental State Exam, *CIBIC* Clinician's Interview-Based Impression of Change, *CDR* Clinical Dementia Rating (Data from Rogers et al. 1998a, b)

3.3.6 Cholinesterase Inhibitor Withdrawal

There is another subtle, but important way in which acetylcholinesterase inhibitors differ. Unlike the occurrence of insomnia and sleep disturbance, this difference and its consequences are rarely appreciated by the practitioner, but have been repeatedly demonstrated in blinded studies which evaluate patients throughout treatment and withdrawal. As mentioned above, cholinesterase inhibitors differ in their induction of acetylcholinesterase. Due to its prolonged half-life, leading to excessive cholinergic stimulation during the night, when acetylcholinesterase activity normally increases and acetylcholine release is very low, in order to permit sleep, donepezil induces marked elevations in CSF acetylcholinesterase protein. In contrast, galantamine produces modest changes. Rivastigmine changes are underestimated because rivastigmine's active metabolite does not leave the acetylcholinesterase binding site for acetylcholine, which blocks measurement of the acetylcholinesterase molecules to which rivastigmine is bound. The effects of 3 months of treatment of Alzheimer's patients with donepezil or galantamine, in a head-to-head study, on CSF acetylcholinesterase, are depicted in Fig. 3.10 (Nordberg et al. 2009). Donepezil, 10 mg, raised CSF acetylcholinesterase 215 %, while galantamine caused a 51 % increase, raising the lowered CSF acetylcholinesterase seen in AD to just above the normal range. A separate study evaluated CSF acetylcholinesterase concentrations before and after treatment of patients with 5 mg as compared to 10 mg donepezil per day for 6 months to a year. Patients on 10 mg donepezil had significantly greater increases in CSF acetylcholinesterase than patients on 5 mg ($p < .02$) (Davidsson et al. 2001). Not surprisingly, and likely as a consequence of the induction of

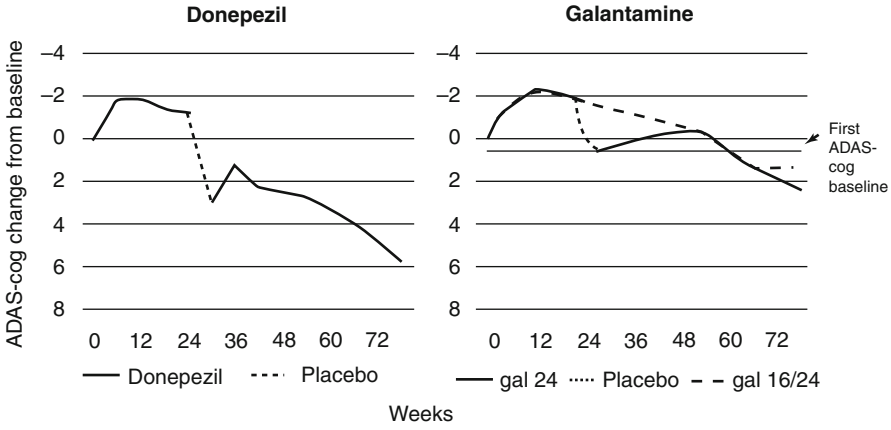

Fig. 3.11 ADAS-cog scores before, during, and after 6-week withdrawals in separate studies of donepezil and galantamine. Donepezil withdrawal caused a fall in scores below the first ADAS-cog, at baseline, which was partially restored by retreatment. Galantamine patients did not decline below the level of their first ADAS-cog (at screening). Retreatment completely restored galantamine patients' scores to those of patients treated continuously, with 16 mg/day, and increased to 24 mg/day at 24 weeks. *ADAS-cog* Alzheimer's Disease Assessment Scale—cognitive, *gal* galantamine (Adapted from Doody et al. (2001), and from data on file)

acetylcholinesterase, a PET study of brain acetylcholinesterase inhibition in humans found no increase in enzyme inhibition in cortex when patients receiving 5 mg donepezil were raised to 10 mg/day (Kuhl et al. 2000). Increasing the donepezil dose apparently induces more acetylcholinesterase. With a much greater amount of enzyme to inhibit, 10 mg donepezil does not produce significantly more inhibition than 5 mg donepezil.

What might be the consequences of very large increases in brain acetylcholinesterase? This is classic pharmacologic tolerance. Thus, a decrease in the drug's effect with time and an exacerbation of symptoms upon withdrawal are expected. The greater the system's adaptation to the drug, in this case, the increase in acetylcholinesterase, the more severe the withdrawal would be expected to be. This is exactly the case with donepezil. Scores on four major outcome measures, ADAS-cog, MMSE, Clinician's Interview-Based Impression of Change, and Clinical Dementia Rating—Sum of Boxes, were nearly identical at the point of donepezil withdrawal in patients on 5 and 10 mg doses, yet the pattern of withdrawal decline was greater in patients having been on 10 mg than on 5 mg for all of these measures (Rogers et al. 1998a) (Fig. 3.11). Nevertheless, it would be expected that upon retreatment, acetylcholine levels would return to those previously achieved during treatment, and patients' performance would be restored. This did not happen. Clinical deterioration following donepezil withdrawal was not completely reversed by retreatment in the open-label phase following initial pivotal double-blind studies, as shown on the left side of Fig. 3.12. According to the investigators, discontinuation of donepezil for 6 weeks and restarting the drug "might not result in patients returning to the

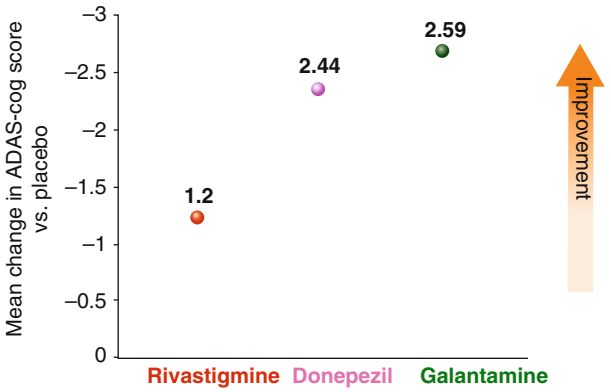

Fig. 3.12 ADAS-cog changes with cholinesterase inhibitors in Japanese phase III 6-month clinical trials in mild-to-moderate Alzheimer's patients. Short-term outcomes with donepezil and galantamine are similar. *ADAS-cog* Alzheimer's Disease Assessment Scale—cognitive (Data from Nakamura et al. (2011), Homma et al. (2008, 2011))

levels of cognition and global function that had been attained before interruption, taking into account the deterioration expected with the passage of time" (Doody et al. 2001). (These observations raise questions about the 23-mg dose of donepezil. The increased dose might be predicted to further increase counter-regulatory acetylcholinesterase production and the withdrawal consequences.) In contrast, galantamine patients withdrawn for 6 weeks return to the cognitive performance of patients who were treated continuously when they enter open-label retreatment, as shown on the right side of Fig. 3.12. Furthermore, unlike donepezil patients, withdrawn galantamine patients' ADAS-cog scores do not decline below the level of their first ADAS-cog, which had been performed at the screening visit, 7 months earlier (Tariot et al. 2000). (The first ADAS-cog in the donepezil study had been at baseline, 5.5 months earlier.) Rogers et al. (1998a). Thus, the irreversible component of withdrawal deterioration in donepezil patients does not occur with galantamine withdrawal.

To further elucidate the withdrawal and retreatment issues associated with donepezil, a study investigating donepezil washout and readministration was performed (Johannsen et al. 2006). Of 812 patients initiating treatment with donepezil open label, 619 remained after 12–24 weeks, 193 of whom did not show cognitive or behavioral benefit. These non-responding patients were randomized to continued donepezil or placebo for 12 weeks, and then donepezil therapy was reinstituted, single blind, for an additional 12 weeks. Behavioral measures during retreatment showed a surprising result. Deterioration on the neuropsychiatric inventory during the placebo phase was not restored by retreatment—the difference between continuously-treated and withdrawn patients was "largely preserved" during retreatment. However, "the difference in DAD scores increased slightly, as the placebo/donepezil group continued to decline further compared with the relative stability

observed in the continuous donepezil treatment group." The deterioration in activities of daily living which had begun during donepezil withdrawal did not abate when donepezil was readministered. The authors note that patients who had been randomized to placebo, when rechallenged with donepezil, "continued to fare worse than those who received continuous donepezil treatment, especially in measures of behavior." They go on to advise that "discontinuing therapy has implications for the caregiver and economic consequences for society" and recommend that "continuous persistent treatment may therefore be the most attractive option."

Realistically, AD patients will discontinue their drug therapy. In a California MediCal registry of 17,742 patients, 67.3 % of 15,128 donepezil and 60.1 % of 2614 rivastigmine patients had discontinued their drug by 431 days (Singh et al. 2005). Hence the persistent behavioral loss and the continued functional deterioration that follow donepezil withdrawal of patients who are not benefitting are adverse events which are not apparent during early dosing, but may be expected nonetheless. The relative ease of initiation of donepezil therapy may be explained by a concomitant rise in acetylcholinesterase, thus limiting early side effects. This same effort on the part of the brain to counteract donepezil's overriding the normal increase in acetylcholinesterase activity during the night is a plausible explanation for its withdrawal phenomena. To avoid donepezil withdrawal, one must avoid donepezil initiation.

There is a biological basis that may explain why patients restarted on donepezil after withdrawal do not achieve their previous levels of function and cognition, even adjusting for disease progression over time. One would expect the same dose of donepezil to restore synaptic acetylcholine to the levels achieved during the pre-withdrawal treatment and for patients to return to expected levels of performance. That they do not suggests that an underlying deterioration may have occurred. Data derived from APP transgenic mice who have had an additional gene for acetylcholinesterase inserted in their genome are an animal model of Alzheimer's disease with the superimposition of increased acetylcholinesterase protein, as occurs to a marked degree with 10 mg donepezil treatment. These animals show significantly increased frequency, burden, and density of amyloid plaques compared to controls with normal acetylcholinesterase, and these changes are apparent as early as 6 months of age (Rees et al. 2003). There are many components of amyloid plaques. Among these components are acetylcholinesterase, which can seed Aβ aggregation (Inestrosa et al. 1996). Thus, it could be anticipated that a multifold induction of acetylcholinesterase enzyme might accelerate the progression of Alzheimer pathology and the formation of toxic oligomers during withdrawal, as is consistent with the deterioration seen during with donepezil discontinuation and the irreversible component of the functional loss.

3.3.7 Tau

Tau is a marker of neuronal degeneration, and phosphotau (ptau), a more specific marker of AD, represents neurofibrillary tangles. CSF tau comes from axonal tau and is believed to represent axonal degeneration. CSF tau levels were significantly

related to levels of neurofilament light, which is an index of subcortical axonal damage, in a large CSF series (Skillback et al. 2013). A significant correlation between CSF tau and acetylcholinesterase protein, as well as between ptau and acetylcholinesterase protein, was found in patients treated with donepezil, 10 mg, for 6–12 months (Vanmechelen et al. 2001). These correlations are consistent with significant increases from baseline in all three biomarkers, acetylcholinesterase protein, tau, and ptau in CSF, after 3 months' treatment with donepezil, 10 mg, as shown in Figs. 3.5 and 3.9 (Nordberg et al. 2009). While tau is a predictor of MCI to AD conversion, a relationship of CSF tau with subsequent decline in AD patients has been found in single-center clinics with long follow-up, but not in the widely dispersed, multicenter Alzheimer's Disease Neuroimaging Initiative population, despite similar numbers of patients (for a review, see Gunnarrson et al.2014). A retrospective study of 72 mild AD patients, followed for a median of 6 years at Uppsala University, found a 5× risk of MMSE decline over 4 points/year in patients in the upper as compared to the lower half of the tau distribution (Gunnarsson et al. 2014). One hundred fifty-one AD patients were followed for 2.0 (1.0–5.0) years at VU University in the Netherlands. Patients with baseline tau in the lowest quintile declined by 1.6 MMSE points per year, as compared to 2.8 points for the highest quintile (Kester et al. 2009). Clinic patients with very elevated tau at Malmo University Hospital had poor cognitive performance at baseline and rapid deterioration over 3 years (Wallin et al. 2010). In contrast, the ADNI analyses, coming from 57 sites dispersed across the USA and Canada, and using different statistical methods, do not show these outcomes. Given the increases in acetylcholinesterase, which is counter-therapeutic, and tau and ptau, predictors of the activity of the Alzheimer process, present at 3 months of donepezil therapy, it is of interest to examine the long-term outcome of these patients.

3.3.8 Long-Term Outcomes in MCI

The longest randomized, placebo-controlled experience with donepezil is a 3-year study in amnestic MCI (Petersen et al. 2005). Multiple outcome measures during this study showed significant differences from baseline in the drug group, as compared with the placebo group until, with one exception, the 18-month time point. Subsequently, the advantages shown by treated patients diminished, until at 3 years, scores were similar in donepezil and placebo patients. Whereas during the first 12 months of treatment the conversion rate to AD from MCI was halved, by month 36 of treatment more than twice as many patients receiving donepezil were converting to AD than were patients receiving placebo (Petersen et al. 2004). In contrast, over a 24-month period of treatment with galantamine the ratio of galantamine to placebo patients converting to AD remained relatively steady between .69 and .83, not a statistically significant reduction (Winblad et al. 2008). As previously noted, galantamine is not approved or recommended for the treatment of MCI. Similar observations have been made regarding the ability of these two drugs to show beneficial effects on structural atrophy in MRI studies. Short donepezil studies reduce atrophy of brain structures on MRI, but these effects disappear in studies longer than 1

Table 3.5 Effects of cholinesterase inhibitors on brain structures as a function of years of treatment

Drug	Study	Time (years)	*n* drug/*n* placebo	Stage of AD/MCI	Hippocampus	Whole brain
Donepezil	Krishnan et al. (2003)	.5	34/44	MMSE 19	[a]	
	Schuff et al. (2011)	1.0	125/105	MMSE 28 CDR 0.5	ns	[a,b]
	Dubois et al. (2012)	1.0	113/109	CDR 0.5	[a]	[a]
	Hashimoto et al. (2005)	1.0	54/93	MMSE 22	[a]	
	Wang et al. (2010)	1.5	18/18	MMSE 25 CDR 0.5	ns	
	Jack et al. (2008)	2.5	37/54	MMSE 28 CDR 0.5	ns	ns
Galantamine	Scheltens et al. (2004)	2.0	142/127	CDR 0.5	ns	[a]

ns no significant effect
[a]Significant beneficial effect
[b]Post-hoc analysis

year. In contrast, galantamine significantly reduced global atrophy in MCI patients at 24 months (Table 3.5) (Krishnan et al. 2003; Schuff et al. 2011; Dubois et al. 2012; Hashimoto et al. 2005; Wang et al. 2010; Jack et al. 2008; Scheltens et al. 2004).

This review of acetylcholinesterase inhibitors indicates that donepezil and galantamine are not equivalent compounds for long-term treatment. Although recently concluded phase III clinical trials in Japan indicate approximate equivalence for these drugs at the 6-month point, donepezil does not maintain its effects on performance, brain structures, or mortality in the long-term, and its withdrawal includes an element of irreversible deterioration (Nakamura et al. 2011; Homma et al. 2008, 2011) Over 1 year, a head-to-head, rater-blinded study of galantamine versus donepezil demonstrated superiority for galantamine in responder rates and MMSE change from baseline (Wilcock et al. 2003). What this review has attempted to make clear is that these drugs differ substantially in the period beyond 1 year; in mortality, withdrawal, and course; and in their early effects on insomnia and its treatment. These differences have practical implications for the clinician and patients and lead to the conclusion that a superiority for galantamine in the long term is becoming apparent. Hence, the question arises as to the best approach for switching patients to galantamine from donepezil.

3.3.9 Switch Studies

There have been several donepezil to galantamine switch studies. Patients who wished to discontinue donepezil for reasons of efficacy, intolerance, or who wanted to try galantamine have participated in protocols with various washout periods and galantamine titration regimens (Rasmusen et al. 2001; Wilkinson et al. 2005;

Engedal et al. 2012; Sasaki and Horie 2014). Ninety-three to ninety-seven percent of these patients were successfully switched to galantamine, regardless of protocol. Cognitive and functional status were either maintained or improved by the end of dose escalation, in marked contrast to the steep deterioration of cognition and function which follows donepezil withdrawal. Side effects, primarily gastrointestinal, were lower during switching than when naïve patients were treated with comparable regimens. Washouts of 0–7 days have been used, with immediate, weekly, and monthly dose escalation. One protocol followed in Japan successfully transitioned patients taking donepezil 5, 8, or 10 mg a day to galantamine 16, 20, or 24 mg a day, respectively, using an immediate switch. Forty-four of forty-six patients successfully switched; the two who did not suffered from overexcitement and anorexia (Sasaki and Horie 2014). Delusions, agitation, and aberrant motor activity were significantly improved compared to donepezil treatment in AD patients ($p < .05$). Prolonged washouts may involve deterioration due to donepezil withdrawal and are not recommended, except in cases of donepezil intolerance, in which case 7–14 days' washout should be implemented (Farlow and Cummings 2007). As with all medications, clinical judgment will guide therapy.

Despite the large number of studies which have been reviewed in this paper, there is a strong clinical lore that surrounds this class of drugs. They are thought to have modest efficacy which decreases with time. This impression is probably driven by donepezil, the most-used cholinesterase inhibitor, which is easy to start and administer due to low side effects and long half-life, but loses efficacy and is damaging to discontinue to the extent that sponsored publications repeatedly caution against it. The large, controlled, 2-year galantamine trial in patients with AD and AD with cerebrovascular disease shows no loss of efficacy over 2 years. The final table in the review, Table 3.6, sets the galantamine data in the context of 2-year donepezil data and 18-month data from a compound recently developed to alter the course of AD, solanezumab (Prnewswire.com 2012). In long-term, placebo-controlled studies, galantamine increased survival and preserved cognition,

Table 3.6 Long-term, randomized, placebo-controlled studies of agents evaluated for Alzheimer's disease (clinical data) and MCI (MRI data)

	Galantamine (2 years)	Donepezil (2 years)	Solanezumab (18 months)
Mortality	↓42 %*	ns	n/a
Cognitive loss	↓48 %*[a]	↓15 %*	↓34 %*
Functional loss	↓25 %*	↓9 %*	ns
Global atrophy	↓34 %* (24 months, MCI)	ns (29 months, MCI)	ns (18 months, AD)
Estimated cost[b]	10 bn	10 bn	100 bn

Data from Hager et al. (2014), Scheltens et al. (2004), Jack et al. (2008), AD 2000 Collaborative Group 2000, Prnewswire.com (2012)

Galantamine is not approved or recommended for patients with MCI

*p values range from .011 to <.0001

[a]Patients on galantamine without memantine

[b]Based on treating the Alzheimer's patients in the USA for 1 year, in billions of US dollars

function, and brain itself to degrees not seen with donepezil, nor with solanezumab. Galantamine should not be used in MCI. However, for patients with AD, or AD with cerebrovascular disease, there is no comparable treatment currently available. Galantamine is a well-known medication which has been used for many years and is relatively inexpensive. It seems that patients with AD or mixed dementia should have the opportunity to be treated with galantamine.

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Practical Pharmacology of Rivastigmine

4

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4.1 Alzheimer's Definition and Treatment Lines

Alzheimer's disease is the most prevalent worldwide neurodegenerative disease (Alzheimer's Association 2015). It is characterized by a progressive cognitive impairment and behavioral disturbances, which lead to functional impairment (Cummings and Cole 2002).

Neuropathological hallmarks of the disease are cortical and subcortical neuronal and synaptic loss, senile plaques, and neurofibrillary tangles, formed mainly by beta-amyloid and phospho-tau deposits respectively.

Alzheimer's disease is also associated with early degeneration of subcortical populations, and therefore levels and function of several neurotransmitters are disrupted. Acetylcholine dysfunction was the first biochemical disorder described in the disease, but also glutamate, noradrenaline, serotonin, histamine, and dopamine are affected. As a result, hippocampus and cortex are deprived of their influence (Simic et al. 2009; Trillo et al. 2013).

Taking into account the described pathophysiology of Alzheimer's disease, one of the main research lines in the treatment of the disease has focused in reducing β-amyloid aggregation by means of decreasing β-amyloid production, increasing its clearance, or inhibiting its aggregation. Another research line has centered in diminishing tau hyperphosphorylation. Although drugs following these strategies could halt or even reverse the disease, none of the ones examined so far has demonstrated clinical benefits. For this reason, only symptomatic drugs that try to restore neurotransmitter deficits are nowadays available. Specifically, acetylcholinesterase inhibitors, which try to normalize acetylcholine levels, and NMDA receptor antagonists, trying to modulate the effects of pathologically elevated glutamate, are the existing ones. In the first group, rivastigmine, donepezil, and galantamine are found, and they are approved for mild to moderate Alzheimer's dementia. In the latter, memantine is the only treatment licensed for moderate-to-severe Alzheimer's disease.

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In the next pages, the characteristics of one of these drugs, rivastigmine, will be developed. Before doing that, biochemical aspects of acetylcholine and the cholinergic role in Alzheimer's disease will be described.

4.2 Biochemical and Physiological Aspects of Acetylcholine

4.2.1 Introduction

Acetylcholine (ACh) was the first neurotransmitter discovered. It was described in 1915 by Henry Hallett Dale for its actions on heart tissue and later confirmed as a neurotransmitter by Otto Loewi, who initially gave it the name "vagus stuff" because of its ability to mimic the electrical stimulation of the vagus nerve. Both scientists received the 1936 Nobel Prize in Physiology or Medicine for their work.

ACh acts at various levels in the nervous system. In autonomic nervous system, it is the neurotransmitter of the preganglionic sympathetic and para*s*ympathetic neurons, of adrenal medulla, of all the parasympathetic innervated organs, and of sweat glands and piloerector muscle of the sympathetic autonomic nervous system. In peripheral nervous system, ACh is the neurotransmitter at the neuromuscular junction between the motor nerve and skeletal muscle. Finally, in the central nervous system, ACh is found primarily in interneurons, although important long-axon cholinergic pathways have also been identified.

4.2.2 Acetylcholine Synthesis and Mechanism of Action

Ach is synthesized in certain neurons by the enzyme choline acetyltransferase (CAT). This enzyme is produced in the soma of cholinergic neurons and transported through the axon to nerve terminal where it is synthesized ACh from the compounds choline and acetyl-CoA. Coenzyme A is synthesized in mitochondria and accesses CAT following transport across the mitochondrial membrane into the cytoplasm. In contrast, choline comes from the liver and dietary sources and is captured from plasma into nerve terminal through a membrane transporter.

However, much of the choline used for ACh synthesis comes from the recycling of choline from metabolized Ach and the breakdown of the phospholipid, phosphatidylcholine.

The rate of ACh synthesis is regulated by precursor availability and by product inhibition, because ACh can bind at an allosteric site on choline acetyltransferase and inhibit the enzyme activity. Once it has been synthesized, a specific transporter uptakes the neurotransmitter from the cytoplasm into vesicles. These vesicles fuse with nerve terminal membrane when an action potential at the presynaptic neuron terminal causes and influx of Ca^{2+}. This way, ACh diffuses into the synaptic cleft and can bind to postsynaptic receptors. Finally, the neurotransmitter is rapidly inactivated by cholinesterase enzymes, mainly by neuronal acetylcholinesterase but also by glial butyrylcholinesterase.

4.2.3 Acetylcholine Receptors and Actions

There are two classes of receptors that bind ACh: nicotinic and muscarinic. Nicotinic receptors bind nicotine and are located at the neuromuscular junction, autonomic ganglia, and sparsely in the central nervous system (CNS). They are ionotropic receptors linked directly to ionic channels and consist of five polypeptide subunits. Their activation causes the opening of the channel, which increases the Na+ movement into the cell and leads to depolarization and generation of the action potential.

Muscarinic receptors bind muscarine and are located at parasympathetic autonomic innervated visceral organs, on the sweat glands and piloerector muscles, and both at postsynaptic and presynaptic level in the CNS. They are G protein-coupled receptors composed of a single polypeptide. Their activation in postsynaptic cells can be either excitatory or inhibitory and is always slow in onset and long in duration.

ACh has excitatory actions at the neuromuscular junction, autonomic ganglion, and glandular tissues and in the CNS. It has inhibitory actions at certain smooth muscles and at cardiac muscle.

4.2.4 Central Nervous System Cholinergic Pathways

Central cholinergic neurons can be subdivided into interneurons and projection neurons. The interneurons are present in the caudate–putamen nuclei, in the hypothalamus, and in the spinal cord. The projection neurons have two important clusters in the brain: the forebrain cholinergic complex (Chaps. 1, 2, 3, and 4) and pontomesencephalotegmental complex (Chaps. 5 and 6).

The forebrain cholinergic complex is formed by medial septum, horizontal and vertical diagonal band of Broca, and nucleus basalis of Meynert. Neurons of the medial septum innervate predominantly the hippocampus; those of the vertical and horizontal diagonal band project to the anterior cingulate cortex and olfactory bulb, respectively; and those of the nucleus basalis of Meynert provide afferents to the amygdala and throughout the rest of the cortical mantle (Bigl et al. 1990). Therefore, the cholinergic neurons of the forebrain complex are important in memory and cognition. The pontomesencephalotegmental complex is formed by the pedunculopontine and laterodorsal tegmental nuclei. Their neurons innervate the pontine reticular formation, the thalamus, the limbic system, the superior colliculus, and the basal ganglia. Consequently, the cholinergic neurons of the pontomesencephalotegmental complex are involved in the rapid eye movement sleep and eye movements, sleep–wake cycle and arousal, stimulus-reward learning, visual orienting, and sensory–motor patterns (Schliebs and Arendt 2006).

4.2.5 Functions of Acetylcholine in the Central Nervous System

Physiologically, the brain cholinergic system is involved in many functions in the central nervous system. It plays a role in controlling cerebral blood flow, cortical

activity, sleep–wake cycle, conscious awareness, behavior, and modulating cognitive function and cortical plasticity (Schliebs and Arendt 2006).

With respect to sleep–wake cycle or circadian rhythm, cholinergic relevance is explained because high cholinergic background activity occurs during wakefulness and rapid eye movement (REM) sleep. This is important also in cognition because REM sleep appears strongly related with episodic memory and circadian rhythms exert important influences on cognitive processes and different sleep stages may support in particular the development of memory consolidation (Van der Zee et al. 2009; Brankačk et al. 2009). Consequently, pharmacological blockade of cholinergic receptors interferes with REM sleep, and restoration of cholinergic activity may yield normalization of sleep–wake patterns. What remains to be confirmed, however, is whether such improved sleep patterns may directly counteract memory deterioration.

Considering conscious awareness, the role of ACH it is easy to understand because 90 % of brainstem projections to the thalamus, one of the most important structures involved, are cholinergic (Bentivoglio 1990).

With regard to behavior, it should be taken into account that the limbic system is a major target for cholinergic innervations (Mesulam 1995). Therefore, cholinergic pathways are related with vegetative and survival behaviors, emotions, learning, and memory (Mega et al. 1997).

Regarding cognitive function, different studies in humans indicate that cholinergic pathways have important functional roles in attention, working memory, and a number of additional mnemonic processes (Perry et al. 1999).

With reference to cognitive function, it has been described the involvement of cholinergic system in learning, memory, and attention (Schliebs and Arendt 2006).

However, the role of ACh in learning and memory is complex and still not fully understood. ACh affects not only one, but possibly all memory systems in different ways, and that it modulates the distinct phases of learning and memory differentially: favoring memory encoding and attention efforts while hampering memory consolidation and retrieval (Van der Zee et al. 2011).

In relation to attention, psychopharmacological, neuroimaging, and psychological studies of cholinergic system functioning in humans show that the cholinergic system has a specific modulatory role in this cognitive function (Perry et al. 1999; Sarter et al. 2006). Deficiencies in attention processing impair discriminatory processes and responsiveness to relevant and new stimuli and, as a result, can cause cognitive deficits. Moreover, some authors hypothesize that central cholinergic impairment delineates a specific central cholinergic deficiency syndrome of behavioral and psychological symptoms in dementia of the Alzheimer's type characterized by psychosis, restlessness, agitation, and mood symptoms (Lemstra et al. 2003).

Finally, the function of acetylcholine in cortical plasticity is possible because it establishes synaptic contacts in networks of cells that will perform complex cognitive functions in adulthood (Berger-Sweeney 2003). Therefore, cholinergic system has been implicated in mediating plasticity in the brain in response to experience or injury. In fact, various animal studies have demonstrated the beneficial effects of cholinergic agonists on enhancing recovery and minimizing neuronal damage in various injury models, the impaired experience-dependent plasticity in the cortex and hippocampus in cholinergic depletion states, the modulation of neurotrophic

factors that play a major role in neuronal survival and plasticity in adulthood by Ach, and the interaction between acetylcholine and estrogen in supporting hippocampal plasticity in aging females (Craig et al. 2011).

4.2.6 Cholinergic Susceptibility in Aging Brain

Although neuronal cell loss was found predominantly in pathological aging, such as AD, normal aging is accompanied by dendritic, synaptic, and axonal degeneration with nearly no cell loss (Burke and Barnes 2006; Coleman 2005; Rapp and Gallagher 1996; Rasmussen et al. 1996; Ypsilanti et al. 2008). These findings suggest that functional decline associated with aging across species does not primarily result from cell loss but other mechanisms including decrements in gene expression, impairments in intracellular signaling, and cytoskeletal transport that may mediate cholinergic cell atrophy leading to age-related functional decline in the brain (De Lacalle et al. 1996; Niewiadomska et al. 2006; Small et al. 2004; Williams et al. 2007).

ACh cells in basal forebrain are the most affected cholinergic cells in Alzheimer's disease. Different studies have shown that these neurons are more susceptible to toxic agents as compared to those in the striatum and brain stem, indicating that brain cholinergic neurons demonstrate differential sensitivity to pathogenic insults (Fass et al. 2000; Julka et al. 1995). Some explanations of the particular vulnerability could be their dependency of acetyl-CoA not only for energy production but also for acetylcholine synthesis, their higher demand for energy production which cause them to be more sensitive to aging-related energy (glucose) deprivation (Szutowicz et al. 2006), AChE-induced expression with acute stress (Li et al. 1996), more susceptibility of transcription factors which are activated by cholinergic stimulation to oxidative stress, the relationship between glucose metabolism and cholinergic transmission (Schliebs 2005), and cholinergic cell susceptibility to inflammatory conditions (Wenk et al. 2000).

4.3 Cholinergic Hypothesis in Alzheimer's Disease

The cholinergic hypothesis appeared in the late 1970 and was based on the findings that a loss of cholinergic activity was commonly observed in the brains of Alzheimer's disease (AD) patients and that acetylcholine (Ach) had a role in learning and memory (Contestabile 2011; Bartus et al. 1982).

4.3.1 Loss of Cholinergic Activity

The loss of cholinergic activity in AD was demonstrated at various levels. Specific cholinergic deficit, involving the nucleus basalis of Meynert projections, hippocampus, and the temporal and the frontal non-motor areas, was consistently found in autopsy material from Alzheimer's patients (Dournaud et al. 1995; Geula and Mesulam 1996). However, cholinergic innervations of the striatum (originating

from striatal interneurons) and of the thalamus (originating in the brainstem) remained relatively intact in the disease (Geula and Mesulam 1999). Moreover, the activity of the enzyme responsible for the synthesis of acetylcholine, choline acetyltransferase (ChAT), was found to be remarkably decreased in pathological samples from the cortex and hippocampus of Alzheimer's patients (Bowen et al. 1976; Davies and Maloney 1976; Perry et al. 1977). Also, other specific markers of the function of cholinergic synapses, the acetylcholine vesicular transport essential to replenish synaptic vesicles (VAChT), depolarization-induced acetylcholine release, and choline uptake in nerve terminals to replenish the acetylcholine synthetic machine, were reduced in the same tissues (Efange et al. 1997; Nilsson et al. 1986; Rylett et al. 1983). Although muscarinic receptor subtypes were not significantly changed in Alzheimer's disease brains (Nordberg et al. 1992; Waller et al. 1986), at least one type of nicotinic receptors, the α-4 subtype, was described as consistently reduced in patient's brains (Burghaus et al. 2000; Schröder et al. 1991). Moreover, trkA, the high affinity receptor of the nerve growth factor (NGF), a survival factor for cholinergic neurons of the nucleus basalis of Meynert, was found to be decreased in these neurons in the brains from Alzheimer's disease patients (Salehi et al. 1996). Furthermore, in aged rats, forebrain cholinergic neurons demonstrated striking reductions in the retrograde transport of NGF, and cholinergic cells that were no longer capable to transport NGF appeared severely shrunken (De Lacalle et al. 1996; Cooper et al. 1994). Correspondingly, neuropathological studies have suggested that the structural components of the limbic network are the primary site of neurofibrillary tangle formation in patients with AD (Braak and Braak 1991; Brun and Gustafson 1976). Thus, according to Braak and Braak theory of progression of AD pathology, neurofibrillary tangles first appear in the transentorhinal cortex and then progress to other structures of the limbic system before finally spreading to neocortical structures in the end-stages of AD (Braak and Braak 1991).

4.3.2 Role of Acetylcholine in Learning and Memory

The association of cholinergic hypofunction with cognition impairment was suggested by different studies showing a correlation of clinical dementia ratings with the reductions in a number of cortical cholinergic markers such as ChAT, muscarinic and nicotinic acetylcholine receptor binding as well as levels of Ach (Bierer et al. 1995; Gsell et al. 2004; Nordberg 1992). Furthermore, it was described that damage of the basal forebrain cholinergic system in autoptic brains was related to the dementia score evaluated from the patient during life (Perry et al. 1996; Wilcock et al. 1982).

Moreover, pharmacological and lesional studies corroborated this role of the neurotransmitter. After first postulation of Deutsch 1971 (Deutsch 1971), other studies with antimuscarinic agents, selective muscarinic antagonists, and centrally acting nicotinic-cholinergic antagonists have shown to impair memory performance in a variety of behavioral paradigms in rodents (Decker and McGaugh 1991; Hunter and Roberts 1988; Levin 1992). Both muscarinic antagonists and nicotinic antagonists have also shown to impair memory performance in monkeys and humans (Terry et al. 1993; Vitiello et al. 1997; Elrod and Buccafusco 1991; Newhouse et al.

1994; Hristensen et al. 1992; Molchan et al. 1992). Similarly, lesion-induced damage to basal forebrain cholinergic system and cholinergic projections to the neocortex in animal models induce cognitive impairments, especially on attention, as well as on learning and memory processes (Sarter and Bruno 1997; McKinney 2005). It should be noted that damage to similar basal forebrain regions in humans (as a result of arterial aneurysms or resection of an arteriovenous malformation) has also been associated with severe memory deficits (Damasio et al. 1985). On the contrary, drugs enhancing central cholinergic function improve the performance of aged patients (Drachman and Leavitt 1974; Drachman 1977) and reverse deleterious effects of anticholinergic drugs (Bartus et al. 1982).

Thanks to cholinergic hypothesis, the primary therapeutic approach to address the cognitive loss associated with AD was the cholinergic replacement strategy. Although studies with muscarinic and nicotinic–cholinergic ligands were unsuccessful, acetylcholinesterase inhibitors (AChEIs) demonstrated a slight reverse of memory impairment in AD patients and finally became the first and almost unique disease specific treatments.

4.3.3 Questioning the Cholinergic Hypothesis

However, later this cholinergic hypothesis has been questioned, and it is no longer believed that the cholinergic depletion alone is responsible for causing AD.

The reasons for this questioning are diverse. Firstly, studies of AD patients indicate that the loss of cholinergic markers cannot be detected in individuals with mild AD and that the cholinergic deficit is not present until relatively late in the course of the disease (Davis et al. 1999). In contrast to patients with advanced AD, in autoptic brain samples of patients with mild cognitive impairment (MCI) and early AD, no decrease in ChAT activity has been observed in a number of brain regions studied (Tiraboschi et al. 2000). Similarly, the number of ChAT-positive and VAChT-positive cells was unaltered in MCI as compared to non-demented controls (Gilmor et al. 1999). In contrast, in hippocampus and frontal cortex of MCI patients, even an increased activity of ChAT has been observed, indicating that the cognitive deficits observed are seemingly not interrelated with ChAT activity (DeKosky et al. 2002). Also in vivo PET studies of MCI and early forms of AD have observed only mild loss of AChE, as revealed by ligands that label AChE (Rinne et al. 2003). Secondly, the benefit of pro-cholinergic therapy on cognitive function in AD and age-related cognitive deficits is modest, and it is not able to stop disease process (Lleó 2007; Drachman et al. 1982). Thirdly, models of muscarinic cholinergic blockade in normal older adults did not replicate all of the cognitive deficits in AD. Specifically, research with muscarinic and nicotinic cholinergic manipulations in healthy subjects and in animals showed that the cholinergic system primarily contributes to effortful attention processes more than memory, the primary deficit in AD (Sarter et al. 2006; Newhouse et al. 2001). Fourthly, age-related changes in sex hormones such as estradiol can affect cholinergic integrity and cognitive processes (Gibbs 2010). Finally, to further complicate the issue, novel data in primates and humans confirmed that cortical cholinergic activity was also decreased by aging (Smith et al.

1999) and that cholinergic deficits were also found in neurodegenerative diseases others than Alzheimer's disease, although not in hippocampus (Perry et al. 1985; Murdoch et al. 1998).

4.3.4 Corroborating the Cholinergic Hypothesis

Nevertheless, some of the conclusions of aforementioned studies appear premature, and there are important facts that can explain these results and that should be taken into account.

The first one is that that upregulation of ChAT in the surviving cholinergic synapses can compensate for early deficits of the neurotransmitter (Craig et al. 2011). The upregulation of hippocampal ChAT in MCI cases may be due to the replacement of denervated glutamatergic synapses by cholinergic input arising from the septum (Mufson et al. 2008). This way, nearly normal cholinergic levels can be detected in the cortex in spite of significant loss of cholinergic neurons. In fact, one study revealed that cognitive deficits are detectable not earlier before at least 30 % of the total cholinergic basal forebrain cells have degenerated (Arendt 1999). The second one is that ChAT or AChE is not rate-limiting cholinergic enzymes. Therefore, they do not reflect exactly the cholinergic function in the living patients (Terry and Buccafusco 2003). The third one is that although the number of cholinergic neurons can be preserved, the dysfunction of these can be detected in early stages. Thus, parameters of cholinergic function such as trkA and p75NTR receptors, acetylcholine release, high-affinity choline uptake, and expression of mAChRs and nAChRs are altered in MCI and early AD (Mufson et al. 2007; Auld et al. 2002; Picciotto and Zoli 2002). Moreover, neurotrophic factors like NGF and BDNF are dysregulated in MCI and AD indicating an enhanced vulnerability of the cholinergic system in AD (Cuello et al. 2007). Accordingly, neurofibrillary degeneration and cell volume loss have been detected in early stages of AD (Sassin et al. 2000; Mesulam 2004). The fourth one is that taking into account that there is an age-related cholinergic denervation, age-matched control subjects used in studies already show cholinergic depletions of the hippocampus, and it can be difficult to demonstrate the loss of cholinergic neurons in AD (Kuhl et al. 1996). Finally, it should be kept in mind that neurochemical analysis in human tissue samples are compromised by unavoidable delays in their postmortem collection that do not exist in animal studies. That is why in vivo imaging methods are important. In fact, they have shown to support the cholinergic hypothesis. Specifically, positron emission tomography (PET) studies indicate that cortical acetylcholinesterase activity is reduced in AD patients, nicotinic receptor deficits are present in early stages of AD and correlate with the level of cognitive impairment, and muscarinic receptors decrease with age and AD in neocortical regions (Kuhl et al. 1999; Nordberg 2001; Zubieta et al. 2001). Moreover, single photon emission computerized tomography (SPECT) studies indicate that the vesicular acetylcholine transporter is reduced throughout the entire cerebral cortex and hippocampus in early onset AD patients.

4.3.5 Reformulating the Cholinergic Hypothesis

Given all this information, it seems that although dysfunction of cholinergic neurons is relevant to explain symptoms seen in AD, it cannot account for all the manifestations of the illness (Pinto et al. 2011). This fact was the origin of the reformulation of the hypothesis by Craig et al. (2011). Its framework is the cofactor theory of McDonald in 2002 that predicts that different risk factors associated with AD have converging effects on hippocampus causing neuronal damage and death accompanied by progressive cognitive decline (McDonald 2002). It is also based on the Ach role in plasticity of brain through mechanisms like neurogenesis, neurotrophic factors, and changes in dendritic branching, which are involved in learning and memory as well as in functional recovery from injury. Considering the demonstrated cholinergic loss in early stages of the disease, this hypothesis proposes that this cholinergic depletion reduces the ability of the brain to compensate for the accumulation of risk factors, whose frequency increase with age. Therefore, in a healthy individual, sub-threshold injury can be unnoticed because of Ach-mediated compensatory mechanisms. However, memory impairment can appear after a major insult (stroke) or when a minor insult (mild ischemia, elevated glucocorticoids, epileptiform activity) occurs in an individual with poor cholinergic projections to the hippocampus (Craig et al. 2011).

Finally, it should be said that the cholinergic hypothesis has not only been described in AD but also in several brain diseases like psychiatric disorders and brain traumatic injury and also in sleep regulation (Arciniegas 2003; Battaglia 2002; Dilsaver and Coffman 1989; Hshieh et al. 2008; Luppi et al. 2006; Raedler et al. 2007). However, no specific treatments following this theory have been approved in these disorders.

4.4 The Interplay of Cholinergic Function and Alzheimer's Pathology

There is a reciprocal relationship between cholinergic function and Alzheimer's disease (AD) pathology. This complex interdependence is important not only to understand the pathophysiology of the disease but also the current and future treatments possibilities. Next, the main known mechanisms of this association will be exposed (Schliebs and Arendt 2006).

4.4.1 Cholinergic Agonists and Amyloid Precursor Protein Processing

There are some evidences of a link between amyloid precursor protein (APP), the originator of neuritic plaques characteristic of AD, and cholinergic transmission. Before describing them, it is appropriate to clarify that there are two alternatives ways in APP processing. One is amyloidogenic and generates β-amyloid peptide by

the sequential action of β- and γ-secretases. The other one is non-amyloidogenic and generates soluble APPα (sAPPα) by the action of α-secretase.

First evidence of the aforementioned link emerged when it was observed that acetylcholinesterase (AChE) colocalized with β-amyloid deposits in Alzheimer's brains (Morán et al. 1993). Another evidence came from studies showing that M1/M3 muscarinic cholinergic agonists increased sAPPα secretion and decreased total β-amyloid formation both in and in vivo in patients with Alzheimer's disease (Müller et al. 1997; Hock et al. 2003). Regarding the relationship between nicotinic–cholinergic agonists and Aβ deposition, it is complex and incompletely understood (Oz et al. 2013). Agreeing with these mentioned reports, inhibitors of AChE were found to increase secretion of sAPPα in both cortical rat brain slices and cell culture (Mori et al. 1995; Racchi et al. 2001), and scopolamine treatment of transgenic Tg2576 mice resulted in increased levels of fibrillar β-amyloid and decreased α-secretase activity (Liskowsky and Schliebs 2006). Neurotrophic growing factor (NGF) signaling has also been shown to influence expression and metabolism of APP and to modulate the cholinergic control of APP processing (Isacson et al. 2002; Haring et al. 1995).

4.4.2 Acetylcholinesterase and Butyrylcholinesterase Relationship with Beta-Amyloid

AChE intervenes not only in APP processing but also in β-amyloid aggregation itself. It seems that the enzyme forms a complex with the protein and increases the neurotoxicity of Alzheimer's fibrils (Alvarez et al. 1998; Reyes et al. 2004). Conversely, β-amyloid increases AChE in vitro through α7-nicotinic ACh receptors, with β-amyloid (1–42) being more potent than β-amyloid (1–40) (Fodero et al. 2004). Butyrylcholinesterase (BuChE) seems also involved in β-amyloid aggregation because its levels correlate positively with amyloid plaques and neurofibrillar tangles in Alzheimer's brains, and there are studies suggesting a role of BuChE in the transformation of β-amyloid into neuritic plaques (Mesulam and Geula 1994; Guillozet et al. 1997).

4.4.3 Cholinergic Agonists and Tau Protein

Several studies have demonstrated that activation of nicotinic Ach receptors, presumably mediated through activation of the α7 subtype, results in a significant increase in tau phosphorylation (Wang et al. 2003). In contrast, muscarinic Ach receptors activation may prevent tau phosphorylation (Wang et al. 2003; Rubio et al. 2006). According with this, chronic nicotine administration to 1-month-old triple transgenic 3xTg-AD mice for 5 months did not change soluble β-amyloid levels but resulted in a striking increase in phosphorylation and aggregation of tau, which appeared to be mediated by p38-MAP kinase (Oddo et al. 2005).

4.4.4 Beta-Amyloid and Cholinergic Function

There is abundant evidence that β-amyloid may trigger cholinergic dysfunction through action on α7 nicotinic receptors, by affecting NGF signaling, mediating tau phosphorylation, interacting with acetylcholinesterase, and specifically affecting the proteome in cholinergic neurons (Schliebs and Arendt 2011). In fact, it has been observed that the severity of neurodegeneration in AD correlates best with the pool of soluble β-amyloid than with the number of insoluble β-amyloid plaques (McLean et al. 1999). Thus, in different cell and animal models, prefibrillar assemblies of β-amyloid have been shown to induce neurotoxicity, electrophysiological changes, and disruption of cognitive function, which may explain why early cholinergic dysfunction occurs before there are substantial plaques in AD (Cleary et al. 2005). In particular, there are studies providing evidence that soluble β-amyloid can inhibit release of ACh from hippocampal slices, decrease the intracellular acetylcholine concentration, decrease activity of choline acetyltransferase, impair M1 muscarinic Ach receptors, desensitize α7 nicotinic receptors at high concentration, and inhibit hippocampal long-term potentiation in brain slices and rat brains in vivo (Kar et al. 2004; Hoshi et al. 1997; Pedersen et al. 1996; Kelly et al. 1996; Dineley et al. 2002; Walsh et al. 2002; Wang et al. 2002).

Furthermore, the NGF receptor p75NTR has been shown to increase the susceptibility of cells to β-amyloid toxicity. Considering that the p75NTR is mainly expressed by basal forebrain cholinergic cells, this could explain the particular vulnerability of these cells to β-amyloid in AD (Perini et al. 2002). Moreover, semiquantitative immunohistochemical study in aged Tg2576 mice revealed a β-amyloid-mediated decrease in cholinergic innervation of cortical blood vessels, which may contribute to the alterations of the cerebrovascular system observed in transgenic Tg2576 mice (Bürger et al. 2009).

4.5 Enhancing Cholinergic Transmission as a Therapy of Alzheimer's Disease

In light of the cholinergic hypothesis as well as the interplay between cholinergic function and AD pathology, different therapeutic approaches trying to restore basal forebrain cholinergic pathways in the disease have been developed.

Nevertheless, the only approved drugs have been acetylcholinesterase inhibitors (AChEIs), which include tacrine, donepezil, rivastigmine, and galantamine. These therapies prevent the hydrolysis of acetylcholine and thus elevate its level in the synaptic cleft and prolong its action on postsynaptic muscarinic and nicotinic receptors (Lane et al. 2004). However, AChEIs produce only modest improvements; a portion of Alzheimer's patients does not respond to this treatment and do not slow the progression of the disease. Several reasons for this failure can be described (Giacobini 2001; Birks 2006). One reason for their modest effect is the narrow therapeutic index of these drugs, which limit the dose because of early side effects. Also, due to the phasic properties of cortical acetylcholine function, it may be

difficult for increased acetylcholine in the synaptic cleft to result in stimulation of postsynaptic receptors independently from presynaptic activity (Hasselmo and Sarter 2011). The ability of presynaptic neurons to respond to signaling may also be reduced by excessive autoreceptor stimulation (Benzi and Moretti 1998). The wide range of response to treatment could be that chronic administration AChEIs may induce compensatory mechanisms at the cholinergic synapse that counteract the desired action of the drugs (Schliebs and Arendt 2006). Lastly, considering the inability to stop the progression of the disease, the reason could be that AChEIs are initiated too late. They are not prescribed until clinical signs of memory loss are present and neuropathological damage likely already present. When AChEIs are prescribed early on in AD, there is more success in slowing the progression of this disorder, but an overall decline in cognitive function still occurs in all patients (Doody et al. 2001). However, few studies have explored the preventative effects of these drugs because their side effects.

Other ways to enhance cholinergic transmission not fully studied include Ach precursors, selective targeting of either AChE or BuChE, M1-mAChR agonists, interrupting α7 nicotinic receptor function, development of drugs that maintain the homeostatic balance between trkA and p75NTR, and NGF gene therapy (Mufson et al. 2008; Tasker et al. 2005; Caccamo et al. 2009; Dziewczapolski et al. 2009). Also, NGF administration, transplantation of acetylcholine-producing cells like fibroblasts engineered to produce acetylcholine, immortalized brain endothelial cells genetically modified to express ChAT and/or the vesicular acetylcholine transporter, neural stem cells with cholinergic acquired characteristics, and conditionally immortal neuroepithelial stem cells could be other ways to ameliorate cholinergic function (Dickinson-Anson et al. 1998; Malo et al. 1999; Doering and Snyder 2000; Grigoryan et al. 2000). Such therapies may not only provide cognitive and behavioral improvements in AD patients but also neuroprotective and neurotrophic actions that could also be beneficial in other forms of dementia and psychiatric diseases like schizophrenia (Terry and Buccafusco 2003).

To conclude, taking into consideration the reformulated cholinergic hypothesis, it seems that enhancing Ach in early stages of the disease could be more effective and even stop its appearance. So, regular testing of ACh levels in the 40–60-year-old population could be helpful to initiate preventative cholinergic therapy as soon as a decline is detected. Moreover, intensifying compensatory mechanisms like doing intellectual and leisure activities or exercise could decrease the chances of developing the disease, also in the absence of a functional cholinergic system, as it has already been shown (Roe et al. 2007). Clearly, therapeutical strategies designed to avoid β-amyloid-mediated neurodegeneration may be successful in preventing or minimizing cholinergic synaptic and neuronal cell loss.

4.6 Acetylcholinesterase Inhibitors

The use of acetylcholinesterase inhibitors (AChEIs) in Alzheimer's disease (AD) patients increases ACh levels in synaptic cleft. As a result, and given acetylcholine (Ach) role in the brain, cognition, function, and behavior of patients can improve.

However, it has been demonstrated that these drugs not only have this action but also are able to induce a marked upregulation and sensitization of α7 nicotinic ACh receptor in prefrontal neocortex (Reid and Sabbagh 2008) and hippocampus (Placzek et al. 2009) and induce the release of other neurotransmitters like noradrenalin, dopamine, or glutamate (Shearman et al. 2006). Both α7 nicotinic Ach receptors and mentioned neurotransmitters are known to be involved in cognition processes.

In general, the use of AChEIs has showed also positive effects on the architecture of sleep in both elderly demented and non-demented people (Hornung et al. 2007; Cooke et al. 2006). Sleep disorders are common in AD and include nighttime sleep fragmentation, increased sleep latency, decreased slow-wave sleep, increased daytime, napping, and episodes of increased confusion, wandering, and anxiety in the late afternoon and evening. Sleep is regulated by neurons of the preoptical area, which inhibit the arousal system, where ACh and noradrenaline play an important role. Thus, ACh release should decrease during non REM-sleep, and it seems that this decrement plays a critical role in the consolidation of declarative memory (Rasch et al. 2006). Due to pharmacokinetic properties, donepezil induces a stable increase of ACh during the whole day, and it can create adverse sleep-related events (insomnia, nightmares), as confirmed by some clinical trials (Burns et al. 1999). However, these adverse effects are attenuated with chronic administration probably because of counterregulatory adaptative mechanisms and can be avoided administering the drug during the day. Galantamine and rivastigmine have less frequently these side effects (Grossberg et al. 2010a; Nieoullon et al. 2008).

Also experimental evidence indicates that AChEIs could induce long-lasting effects beyond the replacement of Ach and play a neuroprotective role, because they can interfere with β-amyloid synthesis and cell death mechanisms like glutamate excitotoxicity, mitochondrial dysfunction and free radical production, and oxidative stress (Pepeu and Giovannini 2009). However, this potential role has not been proved in vivo studies.

Finally, it seems that memantine, a glutamate antagonist, has a higher effect when combined with AChEIs (Geerts 2005). Therefore, probably polytherapy combining AChEIs, memantine, and aminergic, serotoninergic, and dopaminergic drugs is the promising future AD treatment.

4.7 Pharmacodynamic Properties of Rivastigmine

Rivastigmine is a selective, reversible acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitor. Consequently it stops acetylcholine (ACh) breakdown and increases the neurotransmitter levels in synapses and junctions. Thanks to its biochemical structure, rivastigmine can cross the brain–blood barrier and acts mainly in central nervous system. However, a minor proportion of rivastigmine can also act at neuromuscular junction, although its clinical effects are negligible at this level.

Rivastigmine temporarily inactivates the target enzymes by forming a covalently bound complex with them (http://www.ema.europa.eu/docs/en_GB/document_library/

EPAR_-_Product_Information/human/000169/WC500032598.pdf). In vitro rivastigmine is a potent inhibitor of AChE activity and a 100 times more rapidly inhibitor of BuChE activity (Darvesh et al. 2003). As well as inhibiting these enzymes in normal structures (neurons and axons), rivastigmine inhibits them in pathological structures (plaques, tangles, and glia) (Eskander et al. 2005). Therefore, therapeutic concentrations of rivastigmine are likely to inhibit pathological cholinesterases and potentially interfere with disease pathology. Furthermore, as BuChE activity has been shown to increase in AD, contrasting with AChE in altered or reduced activity, and taking into account that rivastigmine inhibits both cholinesterases, this drug may increase ACh levels more effectively than other agents that inhibit only AChE activity (Greig et al. 2001).

Rivastigmine inhibits preferentially the G1 isoform of AChE in the brain (Rakonczay 2003). Taking into account that the level of this isoform remains unchanged in AD, unlike other isoforms that decrease, the G1 predilection can boost the capacity of rivastigmine to increase ACh. Also, bearing in mind that G1 predominates in the brain and G4 in presynaptic membrane of the neuromuscular junction in skeletal muscle, the rivastigmine G1 selectivity may minimize peripheral adverse events relating to the heart and muscle (Weinstock 1999). Finally, given that levels of G1 isoform are highest in the temporal cortex and lowest in the caudate nucleus, rivastigmine shows no impairment of complex movement performance in patients with AD, in contrast with the other AChE (Weinstock 1999).

After a single dose of oral rivastigmine 6 mg in humans, AChE inhibitory activity is detectable in the CSF for 10 h, with maximum inhibition observed 5 h post-dose (http://www.pharma.us.novartis.com/product/pi/pdf/exelonpatch.pdf). Regarding BuChE activity, its plasma activity is reduced with both capsules and patch routes of administration but is more gradually and smooth with the second. Therefore, with rivastigmine capsules, two troughs in plasma BuChE activity were observed with rivastigmine capsules 1.5–6 mg twice daily, the first between 2 and 6 h after the morning dose and the second between 2 and 5 h after the evening dose. With rivastigmine patch, maximum inhibition of BuChE activity was observed 16 h after application of rivastigmine 4.6 mg/24 h patch and 12 h after application of rivastigmine 9.5 mg/24 h patch, with inhibition sustained near peak levels for the remainder of the 24-h application period (Lefèvre et al. 2008).

Studies analyzing the pharmacodynamic properties of rivastigmine transdermal patch in different ethnic groups have shown that Japanese individuals were generally similar to those in healthy white individuals, but that BuChE inhibition was slightly higher in Japanese participants, which may be attributed to the lower bodyweight of these individuals (Lefèvre et al. 2009).

No adverse pharmacodynamic drug interactions have been observed when oral rivastigmine (1–12 mg/day) was administered concomitantly with medications from 22 therapeutic classes, including antidiabetics, antihypertensives, antacids, and antiemetics (Grossberg et al. 2000). Moreover, cholinesterase inhibition by rivastigmine is not affected by concomitant administration of memantine (http://www.pharma.us.novartis.com/product/pi/pdf/exelonpatch.pdf). Also, concomitant administration of oral rivastigmine with digoxin does not adversely affect cardiac conduction, and coadministration with warfarin does not affect the

warfarin-induced increase in prothrombin time (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf; http://www.pharma.us.novartis.com/product/pi/pdf/exelon-patch.pdf). Rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anesthesia; therefore, caution is recommended when selecting anesthetic agents. Rivastigmine should not be coadministered with other cholinomimetic agents, and it may interfere with the activity of other anticholinergic agents (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf; http://www.pharma.us.novartis.com/product/pi/pdf/exelonpatch.pdf).

Rivastigmine is well suited for transdermal delivery because of its low molecular weight (250.34 g/mol) and amphipathic properties, which allow it to pass easily through the skin to the bloodstream (Grossberg et al. 2010a).

4.8 Pharmacokinetic Properties of Rivastigmine

4.8.1 Absorption and Distribution

Oral rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 h. As a consequence of rivastigmine's interaction with its target enzyme, the increase in bioavailability is about 1.5-fold greater than that expected from the increase in dose. Absolute bioavailability after a 3 mg dose is about 36 % ± 13 %. Administration of rivastigmine with food delays absorption (t_{max}) by 90 min and lowers C_{max} and increases AUC by approximately 30 % (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

Absorption of rivastigmine from the transdermal patch is slow, with rivastigmine being detected in the plasma after a lag time of 0.5–1 h after the first dose. Approximately 50 % of the drug load is released from a patch during the 24-h application period. Peak plasma concentrations (C_{max}) are reached in 10–16 h after a single dose, with a slow decrease in concentration over the remainder of the 24-h period. On application of a new patch during multiple dose administration, there is an initial gradual decrease in plasma rivastigmine concentrations until the rate of absorption from the new patch exceeds that of elimination, after which time plasma concentrations increase gradually to reach a peak at 8 h. There is no relevant accumulation of rivastigmine or its metabolite NAP226-90 following multiple dose administration of the patch, with the exception of higher plasma rivastigmine concentrations on the second day than on the first day of patch administration. It should be noted that exposure to rivastigmine and its metabolite NAP226-90 is highest when the patch is applied to the upper back, chest, or upper arm, with exposure levels 20–30 % lower when the patch is applied to the abdomen or thigh (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf; http://www.pharma.us.novartis.com/product/pi/pdf/exelonpatch.pdf).

The main differences between transdermal and oral rivastigmine formulations pharmacokinetic properties are that patches have a more gradual and sustained absorption. Patches have less fluctuation between the maximum and minimum plasma concentrations. Thus, steady-state trough concentrations of rivastigmine are 50 % of peak levels after patch administration, while they are almost zero between the two daily doses with oral administration. Moreover, increments in exposure when rising the dose are less pronounced with the patch. So, C_{max} values are lower, and time to C_{max} values are longer with patches than with capsules. Lastly, single-dose intersubject variability is smaller with transdermal administration than with the oral form (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

There is an approximately linear and inverse relationship between exposure to rivastigmine and its metabolite NAP226-90 and bodyweight of AD patients at steady state. Hence, rivastigmine steady-state concentrations are doubled when bodyweight decreases by half, and they are halved when bodyweight doubles (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

Rivastigmine is weakly bound to plasma proteins (40 %), with an apparent volume of distribution of 1.8–2.7 L/kg. It crosses the blood–brain barrier readily, with peak CSF concentrations observed 1.4–2.6 h post-dose (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

4.8.2 Metabolism and Elimination

Rivastigmine is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the metabolite NAP226-90. In vitro, this metabolite shows minimal inhibition of acetylcholinesterase (<10 %). Half-life in plasma is approximately 1 h for oral rivastigmine and 3.4 h after transdermal patch. The longer $t_{1/2}$ of the patch is explained because elimination is rate limited by absorption (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

Based on in vitro studies, no pharmacokinetic interaction is expected with medicinal products metabolized by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Based on evidence from animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine is approximately 130 l/h after a 0.2 mg intravenous dose and decreases to 70 l/h after a 2.7 mg intravenous dose, which is consistent with the nonlinear, overproportional pharmacokinetics of rivastigmine due to saturation of its elimination. Renal clearance of rivastigmine is 2.1–2.8 L/h. Rivastigmine is metabolized to a lesser extent after transdermal than after oral administration, presumably because of the lack of presystemic (hepatic first pass) metabolism. So, the metabolite-to-parent AUC ratio is around 0.7 after transdermal patch administration versus 3.5 after oral

administration. No unique metabolic routes have been detected in human skin in vitro. Rivastigmine is eliminated by the kidneys mostly as metabolites. Unchanged rivastigmine is found in trace amounts in the urine and feces. Nicotine use increases the oral clearance of rivastigmine by 23 % in patients with AD (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

4.8.3 Special Populations

Age has no impact in bioavailability of rivastigmine in AD. Studies in Alzheimer's patients aged between 50 and 92 years showed no change in bioavailability with age (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

The C_{max} of rivastigmine was approximately 60 % higher, and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects. Renal impairment C_{max} and AUC of rivastigmine were more than twice as high in subjects with moderate renal impairment compared with healthy subjects; however, there were no changes in C_{max} and AUC of rivastigmine in subjects with severe renal impairment. No study has been conducted with rivastigmine transdermal patches in subjects with hepatic or renal impairment (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

No relevant differences in the pharmacokinetics of rivastigmine transdermal patch were observed between Japanese and White healthy individuals (Lefèvre et al. 2009).

4.9 Clinical Evidence Supporting the Use of Rivastigmine

Rivastigmine has shown to be beneficial for people with mild to moderate Alzheimer's disease (AD). In comparison with placebo, improvements have been seen in the rate of decline of cognitive function, activities of daily living, and severity of dementia. There are different doses and routes of rivastigmine. It is available in capsules, transdermal patches, and solution.

Rivastigmine efficacy has been proven in various studies. For the sake of simplicity, in next sections only results of the most robust works of the drug will be exposed.

Regarding capsules, outcomes of a Cochrane review, that included nine unconfounded, double-blind, placebo-controlled, randomized trials with 4775 participants suffering from AD, will be described (Birks and Grimley Evans 2015). Regarding the effects of transdermal patch results of two studies, IDEAL (Investigation of transDermal Exelon in ALzheimer's disease) (Winblad et al. 2007) and OPTIMA (OPtimizing Transdermal Exelon In Mild to-moderate Alzheimer's disease) study (Cummings et al. 2012) will be explained. IDEAL was a 24-week

double-blind placebo-controlled study and had an open-label extension phase. Patients included in this study had a diagnosis of AD with a mean duration of 1.1 or 3.9 years, were aged 50–85 years, had a Mini-Mental State Examination (MMSE) score of 10–20 or 10–24 (mild to moderate compromise) and had a primary caregiver. OPTIMA compared the efficacy and safety of 13.3 and 9.5 mg/24 h rivastigmine patches in patients with AD meeting functional and cognitive decline criteria during an initial open-label phase with 9.5 mg/24 h patch. The analysis investigated the efficacy of 13.3 mg/24 h patch on the autonomy in instrumental activities of daily living. Patients were aged 50–85 years, had a diagnosis of AD, and had MMSE scores of 10–24.

The efficacy of rivastigmine solution will not be discussed in this text because it is equivalent to rivastigmine capsules. Likewise, 17.4 mg/24 h rivastigmine patch is not considered here because its efficacy is not significantly different compared with the 9.6 mg/24 h patch, but it has higher adverse effects (Birks and Grimley Evans 2015).

Next the results of these studies and their impact on different areas involved in AD will be developed. Also the safety, tolerability, and the frequency of adverse effects of rivastigmine will be discussed. Finally, its benefits in Parkinson's disease dementia (PDD) and its possible utility in other pathologies will be explained.

4.9.1 Cognitive Function

Cognitive function impairment is the one of the chore features of AD and PDD and has a great impact in patients and caregivers daily life. Therefore, it is one of the main outcomes of the studies analyzing the efficacy of rivastigmine.

There are different scales available to measure this complex brain function. However, the most frequently used and that were analyzed in the aforementioned studies are ADAS-cog and MMSE. ADAS-cog stands for Alzheimer's Disease Assessment Scale, cognition subscale, and its primary purpose is to be an index of global cognition in response to anti-dementia therapies. It is a clinician-administered 70-point evaluation and assesses multiple cognitive domains including memory, language, praxis, and orientation (Rosen et al. 1984). MMSE stands for Mini-Mental State Examination and is a 30-point scale clinician-administered evaluation and is the mostly used test worldwide for screening and dementia staging (Hashimoto and Mori 2011). Also, other scales that evaluate specific cognitive domains are used as secondary measures in those studies. Trail Making Test part A (TMTA) (Bornstein 1985), a test where consecutive targets numbers on a sheet of paper should be connected in sequential order by the test taker and which evaluates attention cognitive domain, and the Ten-Point Clock-Drawing Test (TCD), which assesses visuospatial and executive functions, are the most used ones (Mendez et al. 1992).

Efficacy of rivastigmine capsules in the improvement of ADAS-cog is shown in the Cochrane review (Birks and Grimley Evans 2015). High-dose rivastigmine (6–12 mg daily) was associated with a two-point improvement in cognitive function on the ADAS-cog score compared with placebo after 26 weeks. Lower-doses capsules (4 mg daily or lower) showed same statistically significant results.

Efficacy of rivastigmine patches was shown in the IDEAL study (Winblad et al. 2007). Treatment with rivastigmine 9.5 mg/24 h patch significantly improved cognitive and global function. The patch was noninferior to rivastigmine 12 mg/day capsules in terms of cognitive improvement. Cognition and global function were assessed through the ADAS-cog at 24 weeks after treatment with rivastigmine patch 9.5 mg/24 h (10 cm^2) and capsules of 12 mg/d compared to placebo. At that time, the two routes of the administration of the drug achieved an increase of up to 4 points in the ADAS-cog. In particular, a retrospective analysis of the study indicated improvements of delayed recall of words, constructive praxis, and ideational and recall of test interactions in capsules vs. placebo and showed better results in the areas of delayed recall of words, naming objects, and fingers and ideational praxis in patches vs placebo (Winblad et al. 2007; Grossberg et al. 2010b). There were also significant improvements in secondary efficacy measures of this randomized trial MMSE and TMTA (Winblad et al. 2007; Grossberg et al. 2010b). Both the capsules and the patch showed improvements of these two subscales with no statistically significant difference between them. No improvements were seen in TCD for both routes of administration (Winblad et al. 2007; Grossberg et al. 2010b). The 24-week results for the assessment tools and the results for clinically relevant responders of this study are summarized in Tables 4.1 and 4.2, respectively.

Table 4.1 Results of the IDEAL 24-week placebo-controlled study (Winblad et al. 2007)

ITT-LOCF population	Rivastigmine transdermal patches 9.5 mg/24 h $N=251$	Rivastigmine capsules 12 mg/day $N=256$	Placebo $N=282$
ADAS-cog			
	($n=248$)	($n=253$)	($n=281$)
Mean baseline ± SD	27.0 ± 10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD p-value versus placebo	−0.6 ± 6.4 0.005*	−0.6 ± 6.2 0.003*	1.0 ± 6.8
ADCS-CGIC			
	($n=248$)	($n=253$)	($n=278$)
Mean score ± SD	3.9 ± 1.20	3.9 ± 1.25	4.2 ± 1.26
p-value versus placebo	0.010*	0.009*	
ADCS-ADL			
	($n=247$)	($n=254$)	($n=281$)
Mean baseline ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD p-value versus placebo	−0.1 ± 9.1 0.013*	−0.5 ± 9.5 0.039*	−2.3 ± 9.4

Negative ADAS-cog changes indicate improvement. Positive ADCS-ADL changes indicate improvement. ADCS-CGIC scores <4 indicate improvement

*$p \leq 0.05$ versus placebo

ITT Intent to treat, *LOCF* Last observation carried forward

Table 4.2 The results of clinically relevant responders from the IDEAL 24-week placebo-controlled study (Winblad et al. 2007)

	Patients with clinically significant response (%)		
ITT-LOCF population	Rivastigmine transdermal patches 9.5 mg/24 h $N=251$	Rivastigmine capsules 12 mg/day $N=256$	Placebo $N=282$
At least 4 points improvement on ADAS-cog with no worsening on ADCS-CGIC and ADCS-ADL	17.4	19.0	10.5
p-value versus placebo	0.037*	0.004*	

Clinically relevant improvement was defined a priori as at least 4-point improvement on the ADAS-cog, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL

*$p<0.05$ versus placebo

Concerning 13.3 mg/24 h patches, a post hoc analysis of OPTIMA study showed that patients that received this patch dose had significantly improved cognition (≥4 points ADAS-cog) at week 24 and at week 48 compared with 9.5 mg/24 h patch (Molinuevo et al. 2015).

It is important to know that switching from another unsuccessful oral acetylcholinesterase inhibitor (AChEIs) therapy to rivastigmine patch is also effective. This was demonstrated in a 6-month, multicenter, observational, efficacy, and tolerability study that included AD patients who had failed to show benefit from previous oral AChEI treatment (lack/loss of benefit or tolerability problems). They were all switched to rivastigmine patch, and 6 months later, 56 % of them stabilized or increased the MMSE score respect to baseline (Cagnin et al. 2014).

Regarding PDD, a placebo-controlled study showed similar response to rivastigmine in patients with this disease compared to those reported in trials of rivastigmine for AD (Emre et al. 2004). In this study, patients in whom mild to moderate dementia developed at least 2 years after they received a clinical diagnosis of Parkinson's disease were randomly assigned to receive placebo or 3–12 mg of rivastigmine capsules per day for 24 weeks. Rivastigmine-treated patients had a mean improvement of 2.1 points in the ADAS-cog score, from a baseline score of 23.8, as compared with a 0.7-point worsening in the placebo group, from a baseline score of 24.3.

4.9.2 Behavioral Symptoms

AD causes also behavioral disturbances, which usually represent a challenge for clinicians (Mitchell et al. 2009). Nevertheless, many studies have searched the effectiveness in this area of rivastigmine, with no satisfactory results.

Behavior is usually valued through the Neuropsychiatry Inventory test (NPI). NPI is a test that evaluates the frequency and severity of 10 or 12 (in its extended version) neuropsychiatric disturbances that occur frequently in dementia. These are "agitation," "irritability," "anxiety," "dysphoria," "hallucinations," "delusions,"

"apathy," "euphoria," "disinhibition," and "aberrant motor behavior" in the 10-item version test. "Sleep and nighttime behavior change" and "appetite and eating change" are added in the 12-item version NPI (Cummings et al. 1994).

The IDEAL study showed no significant changes with the use of this scale at 26 weeks. Therefore, other studies analyzing behavioral symptoms after switching from another inhibitor to rivastigmine detected no changes (with or without the concomitant use of memantine) (Cagnin et al. 2014; Farlow et al. 2010a).

4.9.3 Activities of Daily Living

Activities of daily living are those activities that usually people do during daily life. They are a reflection of subject's autonomy.

In AD two scales are used to evaluate this function: Progressive Deterioration Scale (PDS) (DeJong et al. 1989) and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale (Galasko et al. 1997). PDS is a self-administrated scale for caregivers that examine the ability of patients to accomplish basic (ADL) and instrumental activities of daily living (IADL) in 11 areas. ADCS-ADL is a 54-point scale informant-rated interview of basic and instrumental activities in daily living.

Rivastigmine 6 and 12 mg daily capsules showed improvements in PDS scale, but not 4 mg capsules (Birks and Grimley Evans 2015). In IDEAL study, both routes of administrations demonstrated also improvements in ADCS-ADL scale, as it can be seen in Table 4.1 (Winblad et al. 2007). The retrospective works analyzing this study (Grossberg et al. 2011; Alva et al. 2011) clarified which items ameliorated in each case. Thus, less deterioration in basic activities of daily living (e.g., eating, changing, bathing) was seen with rivastigmine capsules vs placebo and fewer decrements in patient's autonomy (get a drink, dine, shop), with the use of patches vs placebo. There was no significant difference in both routes of administration vs placebo for complex functions. Moreover, rivastigmine was capable to improve the already established functionality alteration in patients.

Concerning 13.3 mg/24 h patches, in a post hoc analysis of the OPTIMA study, the proportion of patients who showed a clinically relevant response (no decline in the ADCS-IADL scale) was the double with 13.3 mg/24 h patch compared to 9.5 mg/24 h patch, both at week 24 and at week 48 (Cummings et al. 2012; Grossberg et al. 2013).

In PDD, studies that have tested this function have showed similar positive results (Rolinski et al. 2012).

4.9.4 Quality of Life of Patients and Carers

Quality of life is an important issue, and it can be directly evaluated through Quality of Life-Alzheimer's Disease scale (QOL-AD) (Logsdon et al. 1999). It is a brief, 13-item measure scale that includes assessments of the individual's relationships

with friends and family, concerns about finances, physical condition, mood, and an overall assessment of life quality.

A multicentre, prospective, observational study with 1509 patients with mild to moderate AD, already treated with rivastigmine 4.6 or 9.5 mg/h transdermal patch, showed a significant improvement in quality of life (indicated by a change of 2.7 and 2.5 points in the mean patient´s and caregiver's QOL-AD) after 2 months of follow-up (Vagenas et al. 2015).

However, the main mentioned studies of rivastigmine do not have direct evaluations of the quality of life. Nevertheless, data exist which suggest an improvement in this important dimension for patients and caregivers. One of this is the decrease in NPI distress subscale with both rivastigmine capsules and patches that was detected in IDEAL study (Winblad et al. 2007; Cagnin et al. 2014). Also, the described amelioration in daily life activities which reduces the need for admission to residential/nursing care can improve caregiver health-related quality of life (Annicchiarico et al. 2007).

4.9.5 Physician-Rated Overall Impression Tests

Overall impression test are useful to determine meaningful effects of a drug. This aspect serves as a useful measure of clinical utility.

One way to measure the effectiveness of rivastigmine capsules and transdermal form is the 7-point Alzheimer's Disease Cooperative Study-Clinical Global Impressions of Change (ADCS-CGIC) score (Schneider et al. 1997). "Marked," "moderate," or "minimal" improvements in ADCS-CGIC scores were observed in 31 %, 37 %, and 28 % of rivastigmine patch, rivastigmine capsule, and placebo recipients, respectively; 27 %, 26 % ,and 39 % of patients were considered "minimally," "moderately," or "markedly" worse in the respective groups, with significant differences between both routes of administration and placebo (Winblad et al. 2007; Dhillon 2011).

4.9.6 Incidence of Adverse Events

Adverse events can only be quantified by clinical interview. They can alert the physician of a possible misuse, and it is important to act accordingly to avoid the loss of compliance. In fact, approximately 7 % of patients on 4 mg/24 h capsules and up to 23 % of those on 6–12 mg/ 24 h capsules discontinue treatment because of its appearance (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf; Rösler et al. 1999).

Side effects occur frequently in both rivastigmine capsules and patches in the first 4 weeks and while increasing the dose (Winblad et al. 2007). The most systemic common adverse effects are gastrointestinal, followed by central nervous system disorders, as it can be seen in Tables 4.3 and 4.4. Other adverse effects occurring frequently (more than 1 in 100) are anemia, constipation, gastritis, nasopharyngitis,

Table 4.3 Adverse reactions in patients with Alzheimer's dementia treated with rivastigmine capsules (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf)

Infections and infestations	
Very rare	Urinary infection
Metabolism and nutrition disorders	
Very common	Anorexia
Not known	Dehydration
Psychiatric disorders	
Common	Agitation
Common	Confusion
Common	Anxiety
Uncommon	Insomnia
Uncommon	Depression
Very rare	Hallucinations
Not known	Aggression, restlessness
Nervous system disorders	
Very common	Dizziness
Common	Headache
Common	Somnolence
Common	Tremor
Uncommon	Syncope
Rare	Seizures
Very rare	Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders	
Rare	Angina pectoris
Very rare	Cardiac arrhythmia (e.g., bradycardia, ventricular block, atrial fibrillation, and tachycardia)
Not known	Sick sinus syndrome
Vascular disorders	
Very rare	Hypertension
Gastrointestinal disorders	
Very common	Nausea
Very common	Vomiting
Very common	Diarrhea
Common	Abdominal pain and dyspepsia
Rare	Gastric and duodenal ulcers
Very rare	Gastrointestinal hemorrhage
Very rare	Pancreatitis
Not known	Some cases of severe vomiting associated with esophageal rupture

(continued)

Table 4.3 (continued)

Hepatobiliary disorders	
Uncommon	Elevated liver function tests
Not known	Hepatitis
Skin and subcutaneous disorders	
Common	Hyperhidrosis
Rare	Rash
Not known	Pruritus, disseminated cutaneous hypersensitivity reactions
General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Malaise
Uncommon	Fall
Investigations	
Common	Weight loss

Adverse reactions in Tables 4.3, 4.4, and 4.5 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data) (http://www.meddra.org/)

Table 4.4 Adverse drug reactions reported in 854 patients with Alzheimer's dementia treated with rivastigmine patches for 24–48 weeks in randomized controlled double-blind placebo-controlled study (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf)

Infections and infestations	
Common	Urinary infection
Metabolism and nutrition disorders	
Common	Anorexia, decreased appetite
Uncommon	Dehydration
Psychiatric disorders	
Common	Anxiety, confusion, agitation, depression
Uncommon	Aggression
Not known	Hallucinations, restlessness
Nervous system disorders	
Common	Dizziness
Common	Headache
Common	Syncope
Very rare	Extrapyramidal symptoms
Not known	Worsening of Parkinson's disease
Cardiac disorders	
Uncommon	Bradycardia
Not known	Atrioventricular block, atrial fibrillation and tachycardia, sick sinus syndrome

Table 4.4 (continued)

Vascular disorders	
Not known	Hypertension
Gastrointestinal disorders	
Common	Nausea
Common	Vomiting
Common	Diarrhea
Common	Abdominal pain and dyspepsia
Uncommon	Gastric ulcers
Not know	Pancreatitis
Hepatobiliary disorders	
Not known	Elevated liver function tests and hepatitis
Skin and subcutaneous tissue disorders	
Common	Rash
Not known	Pruritus, erythema, urticarial, allergic, dermatitis (disseminated)
General disorders and administration site conditions	
Common	Application site reactions (application site erythema, pruritus, edema, dermatitis, and irritation)
Common	Fatigue, asthenia, pyrexia
Rare	Fall
Renal and urinary disorders	
Common	Urinary incontinence

Adverse reactions in Tables 4.3, 4.4, and 4.5 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data) (http://www.meddra.org/)

pneumonia, urinary incontinence, and pruritus. In the post marketing, rivastigmine was also linked to episodes of hypertension, urticaria, hypersensitivity, blister, allergic dermatitis, convulsions, and worsening of Parkinson's disease (http://www.pharma.us.novartis.com/product/pi/pdf/exelonpatch.pdf). However, although statistics of rivastigmine patch do not differ significantly from placebo, data of capsules double in general and even quadruple the incidence of adverse effects compared with placebo. Therefore, patches have fewer adverse effects than capsules. The concomitant use of memantine does not alter this trend (Sadowsky et al. 2005; Figiel et al. 2008; Olin et al. 2010).

Regarding local effects (moderate to severe), these are present only with rivastigmine patch. The most outstanding of them occur more frequently in patients receiving 9.5 mg/24 h doses than in those receiving 4.6 mg/24 h doses. The most prevalent local adverse event is erythema in the application site, followed by itching. However, serious skin reactions like hospitalization, death, disability, or

required persistent intervention have not been reported. Most dermal adverse effects also occur in the first month of starting treatment and decrease in intensity when the patch is removed.

Caution should be taken when prescribing rivastigmine in patients with sinus node or conduction disturbances (sinoatrial block or atrioventricular block), active gastric or duodenal ulcer syndrome, predisposition to urinary obstruction and seizures, asthma, or obstructive pulmonary disease, because cholinomimetics can exacerbate these diseases (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

Similar adverse reactions are seen in patients with PDD treated with rivastigmine. In a placebo-controlled study, rivastigmine capsules (3–12 mg per day) were associated with higher rates of nausea, vomiting, and tremor at 24 weeks (Emre et al. 2004). Adverse reactions reported during clinical studies in patients with PDD treated with rivastigmine capsules are shown in Table 4.5.

Table 4.5 Adverse reactions reported during clinical studies in patients with dementia associated with Parkinson's disease treated with rivastigmine capsules (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf)

Metabolism and nutrition disorders	
Common	Decreased appetite
Common	Dehydration
Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
Common	Hallucination, visual
Common	Depression
Not known	Aggression
Nervous system disorders	
Very common	Tremor
Common	Dizziness
Common	Somnolence
Common	Headache
Common	Worsening of Parkinson's disease
Common	Bradykinesia
Common	Dyskinesia
Common	Hypokinesia
Common	Cogwheel rigidity
Uncommon	Dystonia
Cardiac disorders	
Common	Bradycardia
Uncommon	Arial fibrillation
Uncommon	Atrioventricular block
Not known	Sick sinus syndrome

Table 4.5 (continued)

Vascular disorders	
Common	Hypertension
Uncommon	Hypotension
Gastrointestinal disorders	
Very common	Nausea
Very common	Vomiting
Common	Diarrhea
Common	Abdominal pain and dyspepsia
Common	Salivary hypersecretion
Hepatobiliary disorders	
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
General disorders and administration site conditions	
Very common	Fall
Common	Fatigue and asthenia
Common	Gait disturbance
Common	Parkinson gait

Adverse reactions in Tables 4.3, 4.4, and 4.5 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data) (http://www.meddra.org/)

4.10 Safety and Tolerability

Tolerability is important in order to ensure treatment compliance. It is usually evaluated by the patient's capacity to continue treatment despite their possible adverse effects.

As it can be deduced by minor adverse effects of rivastigmine patch, specifically gastrointestinal ones, this route of administration has demonstrated higher tolerability (Sadowsky et al. 2005; Figiel et al. 2008; Olin et al. 2010). Moreover, the adhesion of the patch on the skin has been proved satisfactory. During the double-blind period of the IDEAL study, 9.5 mg patches were 95 % adherent or "edges just lifting off," and only 4 % of them were "mostly or just hanging half off" or "completely off or detached" (Cummings et al. 2010a). These data are relevant because improving adhesion improves the clinical benefits (Blesa et al. 2007).

Rivastigmine does not require dose adjustment for renal impairment or for liver failure. However, liver disorders may increase the frequency of adverse effects, and patients with severe hepatic impairment have not been studied yet (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf). Thus, in both cases, the drug should be used with caution. Moreover, the body mass index does not seem to influence the frequency of adverse events with the use of patches, although a low body mass could

be a risk factor of occurrence of these unwanted effects using capsules (Lee and Sevigny 2011).

Switching from acetylcholinesterase inhibitor oral drug to the transdermal application has demonstrated good tolerability (Shua-Haim et al. 2008a, b, c, d).

Regarding drug interactions, for its pharmacodynamic properties, rivastigmine should not be administered with other cholinergic substances and can enhance muscle relaxants of succinylcholine type. Metabolic drug interactions appear unlikely, although it can inhibit the metabolism of other substances mediated by butyrylcholinesterase (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

There are no clinical data on pregnancies exposed to rivastigmine and is still unknown whether it is excreted in human breast milk. Therefore, exposure to the drug during pregnancy and lactation is not recommended (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

4.10.1 Risk of Overdose and Death

Symptoms of rivastigmine overdose include nausea, vomiting, diarrhea, hypertension, and hallucinations; bradycardia and/or syncope, associated with malaise or falls, may also occur (Rivastigmine (Exelon) transdermal patch: risk of medication errors 2010).

Most cases of accidental overdose have not been associated with any clinical signs or symptoms, and most patients continued treatment with rivastigmine. However, in cases of asymptomatic overdose, no rivastigmine should be administered for the next 24 h (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

The use of multiple rivastigmine patches can develop nausea, vomiting, and renal failure with disturbed electrolytes resulting in death. Most cases of misuse of the medicine and dosing errors have involved not removing the old patch when putting on a new one and the use of multiple patches at the same time (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

Thus, in order to avoid misuse or dosing errors, patients and their caregivers must be instructed on how to use rivastigmine transdermal patches correctly (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf).

4.11 Rivastigmine Efficacy Compared with Other Cholinesterase Inhibitors

Donepezil, galantamine, and rivastigmine are efficacious for mild to moderate Alzheimer's disease. Despite the slight variations in the mode of action of the three cholinesterase inhibitors, there is no evidence of any differences between them with respect to efficacy.

There is only one randomized, double-blind study in which two cholinesterase inhibitors are compared, donepezil and rivastigmine. Although both drugs performed similarly on cognition and behavior, rivastigmine showed greater benefit in activities of daily living and global functioning (Bullock et al. 2005).

4.12 Rivastigmine in Clinical Practice

Rivastigmine is indicated in mild to moderate AD (Cummings et al. 2015) as well as in treatment of patients with PDD (Rolinski et al. 2012), where it has demonstrated a positive impact on global assessment, cognitive function, behavioral disturbance, and activities of daily living rating scales.

Nowadays rivastigmine exists in oral and transdermal formulations. The commercially available capsules contain 0.5 mg, 1.0 mg, 1.5 mg, 3.0 mg, 4.5 mg, or 6.0 mg of the drug, whereas the solution contains 2 mg/ml. Patches can be found in three dosage strengths: 4.6 mg/24 h, 9.5 mg/24 h, and 13.3 mg/24 h.

The oral dose should be administered twice a day, with breakfast and dinner. The initial dose is 1.5 mg/2 times a day, and it is increased to 3 mg/2 times a day at 2 weeks. Further increases to 4.5 and 6 mg/2 times a day should be based in the good tolerability of the administered dose and at least 2 weeks after the preceding dose. The maintenance dose is 3–6 mg/2 times a day with a maximum of 6 mg/2 times a day.

The transdermal treatment should be started with an initial dose of 4.6 mg/24 h, and if well tolerated, after a minimum of 4 weeks, the dose must be increase to 9.5 mg/24 h (effective daily dose that proved therapeutic benefit). If this dose is well tolerated and after a minimum of 6 months of treatment, a dose of 13.3 mg/24 h should be considered in those who demonstrate cognitive/functional decline (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000169/WC500032598.pdf). The patch is applied once a day to clean, dry, hairless skin, upper or lower back, upper arm, and chest and should not be applied in the same spot at al least every 14 days (Cagnin et al. 2014; Cummings et al. 2010b).

When switching to patch from capsules or oral solution, patients with a total daily dose of <6 mg of oral rivastigmine can be switched to the 4.6 mg/24 h patch. A patient who is on a total daily dose of 6–12 mg of oral rivastigmine can be switched to the 9.5 mg/24 h patch (http://www.pharma.us.novartis.com/product/pi/pdf/exelonpatch.pdf). Patients or caregivers should be instructed to apply the first patch on the day following the last oral dose.

Rivastigmine does not require dose adjustment for renal impairment or hepatic insufficiency but should be used with caution when the patient has one of these conditions. The main adverse effects appear mostly during the initiation of the drug or while the dose is increased. These include above all gastrointestinal effects. The use of transdermal form decreases the frequency of its appearance but otherwise increases the dermal damages. However, dermal problems are usually mild and transient, requiring only the removal of the patch from the zone to stop their damage (Rösler et al. 1999). In fact, patches

are usually preferred above capsules by both patient and caregiver (Blesa et al. 2007).

It is important to keep in mind that the election of the route of the administration should be considered in light of the tolerability and cost of the treatment (Cummings et al. 2015). This decision is essential and should be taken in agreement with the patient and the caregiver and always accompanied with educational aspects.

4.13 Present and Future of Rivastigmine

Recently, the dose of 13.3 mg/24 h was approved for severe AD by Food and Drug Administration in the USA. This decision was based in a randomized, double-blind study called ACTION (ACTivities of Daily Living and CognitION in Patients with Severe Dementia of the Alzheimer's Type) (Farlow et al. 2010b). 13.3 mg/24 h rivastigmine patch demonstrated statistically significant improvement in overall cognition (Severe Impairment Battery) and function (Alzheimer's Disease Cooperative Study-Activities of Daily Living-Severe Impairment Version) vs the 4.6 mg/24 h patch in severe AD patients at week 24. The most commonly adverse reactions observed included application site erythema, fall, insomnia, vomiting, diarrhea, weight loss, and nausea in a higher percentage of patients with the 13.3 mg/24 h dose than patients with the 4.6 mg/24 h dose (http://www.prnewswire.com/news-releases/novartis-exelon-patch-now-fda-approved-to-treat-patients-across-all-stages-of-alzheimers-disease-213414981.html). However, this dose has not been approved by European Medical Agency.

Concerning the use of rivastigmine in other dementias, few data exist. There is some evidence of benefit of rivastigmine in vascular cognitive impairment. However, this conclusion is based on only one large study (Birks and Grimley Evans 2015). The effect of rivastigmine in dementia with Lewy bodies remains unclear. There is no current evidence to support its use in mild cognitive impairment in Parkinson's disease (Rolinski et al. 2012). Also, there is no poolable data for other rare dementias. The result of the impact of rivastigmine in cognitive impairment in frontotemporal dementia, AD in Down syndrome, CADASIL, multiple sclerosis, Huntington's chorea, and PSP is still uncertain (Li et al. 2015). Finally, there are no sufficient data for its clinical utility in autism spectrum disorders (Chez et al. 2004). Therefore, and given its described theoretical benefits, it is necessary to evaluate the possible efficacy of rivastigmine in these and other less frequent diseases with well-designed, double-blind, placebo-controlled, randomized trials.

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Practical Pharmacology of Memantine

5

David G. Wilkinson

5.1 Introduction

Memantine is a noncompetitive, voltage-dependent *N*-methyl-D-aspartate (NMDA) receptor antagonist. It is licensed for the treatment of moderate to severe AD in the USA and EU, represented by patients with a Mini-Mental State Examination (MMSE) score of <20. Memantine can be used in treatment-naive patients, in patients withdrawn from acetylcholinesterase inhibitors (ChEIs), or as an add-on treatment in patients already stabilized on an ChEI, most commonly donepezil. It has a better tolerability profile than the ChEIs and seems to have particular advantages on the noncognitive symptoms related to agitation and language.

5.1.1 Glutamate and Memantine

Glutamate is an excitatory amino acid neurotransmitter found in cortical and hippocampal neurons. Evidence is accumulating to suggest that the sustained presence of synaptic glutamate due to poor reuptake by glial cells may lead to loss of calcium homeostasis within the neuron. During normal synaptic transmission, full depolarization of the membrane occurs when glutamate binds with the N-methyl-D-aspartate (NMDA) receptor after partial depolarization by other ionotropic glutamate receptors, e.g., alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate. This opens the cation channel which, at rest, is closed by a magnesium ion, allowing calcium ions into the neuron. The glutamatergic system in general, and NMDA receptors in particular, may play a significant role in the execution of synaptic dysfunction and neuronal death triggered by amyloid Aβ in AD. This suggests that NMDA receptor antagonists may influence these pathological processes. In fact, memantine, which is an uncompetitive NMDA receptor antagonist, with fast, voltage-dependent blocking properties, is able to selectively block pathological tonic NMDA receptor activation in the presence of soluble Aβ oligomers (Parsons et al. 2007; Albrecht et al. 2008) while preserving

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their physiological transient synaptic activation. Memantine, like magnesium, blocks the cation channel in the resting state; however, the binding of magnesium and memantine to the receptor is voltage dependent. It is postulated that during the chronic partial depolarization of the membrane, caused by the abnormal persistence of glutamate in the synapse and its effects on AMPA receptors, the voltage change causes magnesium to leave the channel, allowing calcium through. However, memantine, which requires a greater potential difference to dislodge it, remains in place blocking the channel until full depolarization from a physiological stimulus occurs. Thus, while blocking the abnormal leakage, it allows normal synaptic transmission. Chronic excessive calcium influx impairs neuronal homeostasis causing eventual neurodegeneration and may result in synaptic or dendritic damage, necrosis, or apoptosis resulting in cell death (Cacabelos et al. 1999; Lancelot and Beal 1998; Greenamyre and Young 1989). The excessive stimulation of the NMDA receptor, under conditions of energy deprivation such as ischemia and the resulting excitotoxicity, will impair long-term potentiation, a process necessary for memory and learning. Therefore, this hypothesized mode of action of memantine could provide both symptomatic improvements and long-term neuroprotective effects.

5.1.2 Effects of Memantine on Neurodegeneration

Preclinical studies have shown an extensive array of effects that demonstrate a neuroprotective effect for memantine in vitro and in animal models. In various studies memantine has been shown to protect neuronal cells against toxicity due to mitochondrial dysfunction and chronic neuroinflammatory effects on cholinergic neurons and to protect cholinergic neurons after NMDA-induced lesions. In animal models memantine can prevent neuronal damage, preserve acetylcholine terminals, and reduce Aβ-induced learning deficits. It can protect against Aβ-induced apoptosis and neurotoxicity in rat brains and reduce tau phosphorylation in AD-like models possibly by its effects on stimulating protein phosphatase 2a which is known to prevent tau phosphorylation. Whether any of these effects are relevant in patients is unknown, and its neuroprotective potential remains to be confirmed in clinical studies (Miguel-Hidalgo et al. 2002; Li et al. 2004).

However, several clinical trials have proven beneficial symptomatic effects of memantine in studies of AD (Reisberg et al. 2003; Tariot et al. 2004; Peskind et al. 2006), and meta-analysis of several trials suggests potential to reduce clinical worsening (Wilkinson and Andersen 2007; Weiner et al. 2011; Wilkinson 2012).

Interestingly in its early development, its mode of action and potential neuroprotective effect were seen as being relevant to the treatment of the ischemia related to vascular dementia (VaD), but early trials while showing some cognitive benefits were ultimately insufficiently positive to prompt further development for this indication.

5.2 Memantine in Vascular Dementia

Two studies have been published in VaD which had very similar designs. The MMM 300 study was a 28-week multicenter double-blind study conducted in France, which enrolled 321 patients with mild to moderate dementia (using DSM-III and MMSE 12–20) satisfying the criteria for probable VaD according to NINDS-AIREN criteria (Orgogozo et al. 2002). Patients with AD were excluded according to the protocol.

Overall the results were rather equivocal finding statistically significant improvements only on cognition using the Alzheimer's Disease Assessment Scale cognitive portion (ADAS-cog) and MMSE although with some numerical advantage for memantine in all parameters. As has become familiar in subsequent VaD studies, the placebo group showed a lack of the deterioration normally seen in AD trials. Although there was a significant advantage for memantine in the cognitive subscale of the GBS, a composite measure of cognition and function, overall the GBS, the clinical global impression of change (CGIC) and nurses geriatric observation scale (NOSGER) all failed to show a significant advantage for memantine.

The authors argue that the demonstration of a cognitive advantage in a VaD population was a proof of concept and that the lack of decline in the placebo group may have meant that the study was underpowered leading to the equivocal results. This is something of a recurring theme in the memantine data set.

However, as a result of this argument, recruitment for the second study which was already underway was extended (MMM 500), perhaps giving the chance to test that assumption. In this study 548 patients were randomized to either 20 mg memantine daily or placebo in a 28-week multicenter study in the UK (Wilcock et al. 2002). The same entry criteria were used for probable VaD, but the mean MMSE at entry was slightly higher (range 10–22). The results were similar showing that, while there was some slight advantage for memantine in a number of sub-analyses, the only significant outcome was in cognition as determined by the ADAS-cog. The MMSE in the placebo population did not change over the 28 weeks, as predicted in this VaD population, but unfortunately neither did the MMSE in the memantine group.

Again subgroup analysis showed that there were greater benefits for memantine by grouping the patients with more severe dementia as defined by entry MMSE and with small vessel disease on imaging. This latter finding was confirmed in a combined analysis of the two studies when the baseline CT/MRI findings were separated into those with larger cortical infarctions, or large vessel disease, and those with white matter lesions and lacunes, or small vessel disease (Möbius and Stöffler 2002). Those with small vessel disease showed progressive decline in cognitive function compared with the large vessel group who showed no change after 28 weeks, and as a result, the symptomatic improvements were much greater in the small vessel group. This may suggest that while stoke and multiple infarctions are a risk factor for dementia, they represent brain damage rather than dementia, and the cognitive decline we see in VaD patient is caused by

small vessel disease. It was then felt that there could be a rationale for treating more severe AD, and the most influential memantine study was undertaken in a group of moderately severe AD.

5.3 Memantine in AD

AD is defined by the pathological presence of amyloid plaques and neurofibrillary tangles in specific areas of the brain, but this is clearly only part of the story when it comes to the organ failure we see in patients with dementia. The processes which cause this failure are multiple, overlapping, and influence each another.

In AD dementia pathogenesis amyloid Aβ accumulation, excitotoxicity at NMDA receptors, formation of tau neurofibrils, disturbance of mitochondrial function, neuroinflammation, and small vessel disease all play a part.

Memantine has demonstrated neuroprotective qualities in a number of model systems, both in vivo and in vitro. Prevention of NMDA and glutamate-induced cell death has been shown in a number of culture systems, including rat retinal ganglion and cerebellar, cortical, mesencephalic, and hippocampal neurons. Interestingly, in other tissue culture experiments, memantine reduced tau hyperphosphorylation and promoted non-amyloidogenic APP processing. These effects may or may not translate to the patient with brain failure causing dementia and if so may explain some of the observed efficacy of memantine in patients with AD. Other studies have shown memantine has reduced cell loss in rat models of AD (Danysz and Parsons 2012), but it has not been shown to reduce brain atrophy in AD patients (Wilkinson et al. 2012).

5.3.1 Clinical Trials

5.3.2 Moderately Severe AD

Nine randomized controlled trials of memantine in AD have been completed to date, 7 of which have been of 6 months duration (Table 5.1). The first controlled trial to report positive findings in AD was a study of mixed dementia and unlike the others was of 12 weeks duration, undertaken in a severe nursing home population (mean baseline MMSE 6.3) and only tested 10 mg daily rather than the currently licensed dose of 10 mg twice daily used in the others (Winblad and Poritis 1999). This study undertaken in Latvian nursing homes included 166 patients of whom 51 % had AD and 49 % VaD. The primary outcome measures were the CGIC as rated by a physician and the behavioral rating scale for geriatric patients (BGP) subscore "care dependence" as rated by a nurse. The overall outcomes of the study demonstrated a statistically significant advantage for memantine over placebo for both primary outcomes with 73 % of the memantine-treated patients improving on CGIC compared with only 43 % of the placebo group. After a responder analysis, the functional improvements were judged to be clinically relevant. A separate analysis of the AD patients which in fact only amounted to about 20 patients in each

Table 5.1 Overview of phase III trials of memantine in AD

Study	Duration/design	Study population		Efficacy scales included		
		MMSE inclusion	n (ITT)	Cognition	Function	Global status
MEM-MD-10	24-week, DB, PC	10–19/10–22	MEM 126/201	ADAS-cog	$ADCS\text{-}ADL_{23}$	CIBIC-Plus
Peskind (2006)			PBO 140/202			
LU-99679	24-week, DB, PC	11–19/11–23	MEM 166/318	ADAS-cog	$ADCS\text{-}ADL_{23}$	CIBIC-Plus
Bakchine and Loft (2008)			PBO 76/152			
MEM-MD-12	24-week, DB, PC, receiving ChEIs[a]	10–19/10–22	MEM 151/217	ADAS-cog	$ADCS\text{-}ADL_{23}$	CIBIC-Plus
Porsteinsson et al. (2008)			PBO 146/216			
MRZ-9605	28-week, DB, PC	3–14/3–14	MEM 126/126	SIB	$ADCS\text{-}ADL_{19}$	CIBIC-Plus
Reisberg et al. (2003)			PBO 126/126			
MEM-MD-01	24-week, DB, PC	5–14/5–14	MEM 171/178	SIB	$ADCS\text{-}ADL_{19}$	CIBIC-Plus
van Dyck et al. (2007)			PBO 165/172			
MEM-MD-02	24-week, DB, PC, receiving donepezil	10–14/5–14	MEM 104/202	SIB	$ADCS\text{-}ADL_{19}$	CIBIC-Plus
Tariot et al. (2004)			PBO 124/201			
IE-2101	24-week, DB, PC	5–14/5–14	MEM 100/207	SIB-J	$ADCS\text{-}ADL_{19}$-J	CIBIC-Plus-J
Homma et al. (2007)			PBO 107/107			
LU-10116	16-week, DB, PC	5–18/5–18	MEM 124/128	SIB	$ADCS\text{-}ADL_{19}$	–
Chen et al. (2007)			PBO 125/130			
MEM-MD-22	24-week, DB, PC	5–18/5–18	MEM 132/132	BGP-Cog	BGP-Dep	CIBIC-Plus
Forest (2006)			PBO 131/131			

AD Alzheimer's disease, *ADAS-cog* AD Assessment Scale, cognitive subscale, *ADCS-ADL19/23* 19-/23-item AD Cooperative Study, activities of daily living scale, *BGP-Cog/Dep* Behavioral rating scale for Geriatric Patients, cognitive/care dependency subscale, *ChEI* cholinesterase inhibitor, *CIBIC-Plus* Clinician's Interview-Based Impression of Change plus caregiver input, *DB* double blind, *ITT* intention to treat, *J* Japanese language version, *MEM* memantine, *MMSE* Mini-Mental State Examination, *n* number of patients, *PBO* placebo, *PC* placebo-controlled, *SIB* Severe Impairment Battery

[a]Patients already receiving stable doses of donepezil, rivastigmine, or galantamine

group showed an advantage for memantine which was used to support the licensing applications for moderate to severe AD along with the data published by Reisberg (Reisberg et al. 2003). This study was a 28-week double-blind placebo-controlled trial of 252 moderately severe outpatients (mean baseline MMSE 7.9) undertaken in the USA. The main outcome measures were the severe impairment battery (SIB), a cognitive scale validated to demonstrate change in severe AD patients, the Clinicians Interview-Based Impression of Change plus caregiver information (CIBIC-plus), the 19-item Alzheimer's Disease Cooperative Study severe activities of daily living scale (ADCS-ADL), and the functional assessment staging tool (FAST). Other measures, including the MMSE, neuropsychiatric inventory (NPI), and a resource utilization scale, were also used. There were significant advantages for the treated group on the SIB, ADCS-ADL, and FAST. Sub-analysis of the NPI showed a significant advantage for memantine in the domains of delusions and agitation/aggression. This study was important in showing that a new therapeutic agent different from the cholinergic drugs had a clinically significant effect and that these benefits could be achieved in the more severe stages of the disease. Also crucial when generalizing the trial data to clinical practice was the fact that while there was a clear advantage for the treated patients nevertheless at this advanced stage, all patients were deteriorating. This is important when treating patients clinically when one has no placebo group for reference as one has to consider that despite continued decline, the patient may be getting the benefit of a slowed rate of deterioration.

The other published trial of memantine in moderately severe dementia, a 26-week double-blind placebo-controlled study, was in 404 patients who were already stabilized on donepezil (Tariot et al. 2004) The patients had to have been on donepezil for at least 6 months and a stable dose for 3, but in fact the mean length of treatment was 2.5 years with nearly 90 % on treatment for over 1 year prior to entry. The outcome measures were SIB, ADCS-ADL$_{sev}$, CIBIC-plus, NPI, and the BGP care dependency subscore. In this study the patients who were slightly less severe than in the two previous studies (mean baseline MMSE 10) and those that had memantine added to their donepezil showed significant improvements over those patients who continued donepezil with placebo on all measures. Patients on memantine and donepezil treatment compared with donepezil monotherapy also sustained improved cognitive performance relative to baseline compared with a progressive decline in the latter group over the same duration of treatment

The last study in moderately severe AD, similar in design to the study published by Reisberg, was also conducted in the USA, and according to press releases, this did not reach significance though the data has not yet been published for wider comment.

5.3.3 Mild to Moderate AD

Two studies have studied memantine monotherapy against placebo in mild to moderate AD.

The first, a 24-week randomized double-blind parallel group study, of memantine 20 mg/day (10 mg b.d.) or placebo, in 403 US outpatients (MMSE scores of

10–22 mean 17.3), used the ADAS-cog and the CIBIC-Plus as primary outcomes and also measured the ADCS-ADL and NPI. Although this was a monotherapy study, 62 % had been on acetylcholinesterase inhibitors (AChEIs) prior to study. There was no difference in completer rates between groups and those that stopped did so twice as often for poor response than for tolerability. The study showed significant improvements in the primary outcomes ADAS-cog, CIBIC-plus, and in behavior (NPI), but not in function (ADCS-ADL).

The second study in mild to moderate AD was conducted in 470 patients with probable AD in 65 sites in 12 countries in Europe and was an identical design but for ethical reasons used a 2:1 randomization of memantine to placebo. This may have influenced the power of the study as in this case the placebo group showed very little decline in cognition over 6 months, and so although there was a trend in favor of memantine on the ADAS-cog which was significant at 12 and 20 weeks, this did not reach significance at end point (Bakchine and Loft 2008).

In this study, as in the other mild to moderate study, many patients had had prior treatment with AChEIs.

The third mild to moderate study was a placebo-controlled "add-on" study, this time adding memantine or placebo to patients already stable on donepezil rivastigmine or galantamine. This did not achieve statistically significant end points in favor of the memantine group.

A combined analysis of all 6 months studies has been presented separately (Doody et al. 2007). In this analysis the three mild to moderate studies which used the ADAS-cog were combined separately from the three moderately severe studies which used the SIB. Consistent with the results of the published studies, memantine-treated patients with AD showed statistically significant benefits compared to placebo-treated patients on the SIB total score and on the ADAS-cog total score, suggesting a benefit of memantine on cognition throughout the course of AD. Single-item and subscale analyses of the ADAS-cog and SIB showed statistically significant differences between memantine and placebo on: Commands, Orientation, Comprehension and Test Instructions (ADAS-cog) and Language, Memory, Orientation, Praxis, Construction, and Visuospatial Ability (SIB). Memantine significantly improved orientation and language abilities in AD patients. The findings support the efficacy of memantine in improving the patients' ability to communicate and interact with their environment, as well as their comprehension of spoken language which has been reported anecdotally from naturalistic treatment.

5.3.4 Responder Analyses

In clinical trials for AD, efficacy is typically measured using between-group mean differences in terms of change of score on various assessment scales. While these data are valuable, a fuller picture is achieved using supplementary responder analyses, which allow for a better understanding and interpretation of clinically meaningful differences. The European Medicines Agency recommend that responder analyses be performed using a justified definition of response based on

consideration of the natural progression of the disease for the specific setting (EMA 2008). In AD, the responder analyses should assess change of symptoms in the three core domains and should take into account the clinical relevance of the outcome and the disease stage (EMA 2008).

Responder analyses initially focused on the temporary symptomatic improvements produced by pharmacotherapy in mild AD. In this progressive disease, however, achieving stabilization of a patient's condition is a desirable and realistic treatment goal (Winblad et al. 2001; Geldmacher et al. 2006). Consequently, in advanced stages of AD, responder analyses have focused on the ability of pharmacotherapy to reduce the incidence of clinical worsening. Wilkinson and Andersen developed a novel form of responder analysis in which patients are classified according to criteria for clinical worsening, rather than improvement (Wilkinson 2012). "Marked clinical worsening" was defined as concurrent worsening in the cognitive, functional, and global domains over 6 months: a decline of ≥4 points on the AD Assessment Scale, cognitive subscale (ADAS-cog) or ≥5 points on the Severe Impairment Battery (SIB), plus any decline on the AD Cooperative Study, ADL scale (19- or 23-item version; ADCS-ADL$_{19/23}$), and the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). In the cognitive domain, this definition is intended to represent the average natural decline observed in patients with moderate to severe AD over 6 months, which can be considered as clinically significant worsening. The analysis included a subpopulation of patients with baseline MMSE <20 from six pivotal studies (6-month, phase III, randomized, double-blind, placebo-controlled trials [RCTs]); memantine statistically significantly reduced the incidence of marked clinical worsening, versus placebo. In a more recent analysis including a further three RCTs, similar results were observed in favor of memantine (Hellweg et al. 2012).

However, in this study a response in individual domains was not considered, and the rationale for selection of the low cut-off value ("any decline") for clinical worsening in the functional domain was arbitrary. The German Institute for Quality and Efficiency in Health Care (IQWiG) has questioned the relevance of the EMA clinical worsening analysis and recommended the use of a data-driven approach, in the absence of validated or established minimally important differences (MIDs), to determine clinically meaningful worsening.

A further study using an alternative definition of clinical worsening based on established MIDs, if available, and if not, an MID was estimated as half of the pooled standard deviation (SD) of the change in score from baseline to endpoint from the clinical data. This represented a more realistic functional decline in advanced stages of the disease. Using these new, more stringent definitions, the study showed memantine reduces the incidence of clinical worsening in all the key symptomatic domains—cognition, function, and global status—in moderate to severe AD. Furthermore, memantine reduces the incidence of triple clinical worsening, based on a combination of these domains, in moderate AD and in severe AD (Wilkinson et al. 2014).

The results of this study add to the extensive existing evidence in favor of memantine for reducing clinical worsening in moderate to severe AD over 6 months. These

results, when considered together with evidence from long-term observational studies (in patients with existing ChEI therapy), support the clinical view that memantine allows patients to remain independent for longer, alleviating caregiver burden and delaying the time to placement in a nursing home (Wilkinson et al. 2014).

5.3.5 Safety and Tolerability

Overall the tolerability of memantine has been very good in all the trials reported with little difference between memantine and placebo in adverse events and high completer rates. The fact that glutamate is an excitotoxic neurotransmitter and that in the Reisberg trial there was a slight increase in hallucinations $n=11$ [8.7 %] in the memantine group as against $n=4$ [3.2 %] in the placebo group, and insomnia $n=13$ [10.3 %] vs $n=10$ [7.9 %] in placebo group raised some concern. However, the numbers were very small, and any concerns that use of memantine may increase neuropsychiatric symptoms have not been borne out in the subsequent studies. What was of considerable interest, however, was that agitation seemed to be much less frequent in the memantine group $n=23$ (18 %) than in the placebo group $n=40$ (32 %), and subsequent post hoc analyses of the combined trial data seem to indicate that memantine may exert a protective effect against the emergence of psychosis and agitation in AD. However, a short 6-week study of patients with significant agitation as measured by the Cohen and Mansfield agitation inventory (CMAI) failed to show any effect on the CMAI although it showed a significant reduction in the NPI. The CMAI is not a specific dementia scale and as such may not be a useful measure of clinical agitation in AD (Fox et al. 2012).

Another important safety finding from the two studies where memantine was used in conjunction with ChEIs was that there appear to be very few cholinergic side effects overall and that in the Tariot study where all the patients were taking donepezil there was a reduction in diarrhea and fecal incontinence suggesting that it may have effect on reducing the gastrointestinal side effects of ChEIs which lead to further analyses of the combination trial data.

5.4 Effects of Memantine in Combination with ChEIs

Since memantine and ChEIs have different and complementary mechanisms of action, together they potentially offer additional benefits to the patient, and one review of all published studies concluded that treatment with memantine/ChEI combination therapy in moderate to severe AD produces consistent benefits that appear to increase over time and that are beyond those of ChEI treatment alone (Gauthier and Molinuevo 2013).

In a more recent study, RCT data from the Porsteinsson and Tariot studies, where memantine was added to patients stable on ChEIs were combined, testing the hypothesis that low power and baseline heterogeneities caused the divergent results between them, which potentially obscured significant memantine treatment-related

benefits in patients with mild to moderate AD. In this meta-analysis, the efficacy of memantine 20 mg/day versus placebo in patients receiving stable doses of donepezil (10 mg/day) was assessed in two subgroups: moderate to severe AD (MMSE 5–19) and moderate AD (MMSE 10–19) (Atri et al. 2013).

The rationale for choosing these patient subgroups was that they represent the current approved indication of memantine in the EU (moderate to severe AD) and the overlap of the approved memantine and donepezil indications in the EU (moderate AD). MMSE was used as a subpopulation staging surrogate measure to delineate mild (MMSE ≥20) from moderate (MMSE 10–19) and severe (MMSE <10) stages of AD. The study was limited to those patients receiving 10 mg/day of donepezil, the most commonly used ChEI in these trials. ChEIs other than donepezil were excluded.

The analyses in this study compared the efficacy of memantine versus placebo across individual domains of AD, in reducing the occurrence of marked clinical worsening and the tolerability profile of memantine versus placebo.

At week 24, in both the moderate to severe and the moderate subgroups, patients receiving memantine added to donepezil significantly outperformed those receiving placebo added to donepezil in measures of cognition, function, and global status. Also in both subgroups, significantly fewer patients receiving memantine added to donepezil showed marked clinical worsening than those receiving placebo added to donepezil. The incidence of adverse events was similar between treatment groups.

These results support and extend previous evidence that combination treatment with memantine added to stable donepezil in patients with moderate and moderate to severe AD is associated with significant benefits in reducing 24-week decline in cognition, function, and global status. Combination treatment produces substantially reduced rates of marked clinical worsening, has good safety and tolerability, and generates effect sizes that are both statistically significant and clinically meaningful.

5.5 Clinical Use

Memantine is an important and interesting addition to the available treatments for AD. There is now a growing body of evidence particularly in moderate to severe AD, with some supporting evidence for an effect on patients with small vessel disease VaD and PD that confirm an effect on dementia symptoms more generally. The neuroprotective effects shown preclinically remain to be proved clinically, but further analysis and studies may elucidate this in time. There is no doubt that memantine at licensed doses of 10 mg twice daily is particularly well tolerated, and higher doses (28 mg once daily) have been used with effect and without significant worsening in tolerability (Grossberg et al. 2013).

At present there is not enough evidence to decide whether memantine should be started prior to cholinesterase inhibitors in the early stages of AD as findings from the studies in mild to moderate AD have not been as robust as those for the ChEIs. Therefore in most clinics which are seeing patients earlier and earlier in the dementia process, it is usual practice to start an CHEI at a time when attention and memory

are the key symptoms and add memantine later when behavioral symptoms start to emerge. It may be that, as there is a suggestion from the studies that memantine-treated patients show a lower emergence of these behavioral symptoms, it should be started earlier. The practice of holding something in reserve, as many clinicians like to do, to give them a new intervention they can introduce later may be seen as more to satisfy the clinicians need to be helpful than in the patients long-term best interests. Equally although post hoc analyses indicate that the combination of memantine and donepezil is more effective and further reduces clinical worsening than monotherapy, there are no prospective data to indicate whether the two treatments should be started together or whether the two treatments have an additive or synergistic effect when combined. Memantine does however offer a clear treatment option in patients who cannot tolerate AChEIs or in whom their efficacy is in doubt. The pharmacokinetics of memantine: it is 100 % bioavailable; absorption is unaffected by food; and it rapidly diffuses across the blood–brain barrier and has an elimination half-life of 60–80 h making it an ideal for administration once daily. This is of importance in those older frailer and more forgetful patients where once daily dosing would be an advantage. It has a remarkable good safety record at the currently recommended doses, and quicker titration than that recommended on the data sheets is not problematic and often undertaken. One observation that may lead to higher doses being used is that while there are a number of notably positive outcomes in the studies an equal number seem to have just failed to reach significance in the some of the measures used. The usual conclusion drawn is that this suggests a modest effect of the drug, but in view of the very good safety profile supported by many years use, it might suggests that the dose of 20 mg daily is at the borderlines of efficacy and more positive outcomes could be achieved with higher doses. The only adverse event that is occasionally seen in the clinic rather than clinical trials is constipation, which may be less problematic in combination with CHEIs. The study of 28 mg did show positive findings without compromising the impressive tolerability profile. Clinicians often see memantine as a specific treatment for the restlessness, anxiety agitation, and nocturnal wandering that is so problematic for carers, and although this has not been specifically proven, we know the CHEIs are not effective in these areas, and so this again leads us to the position that despite the clear lack of prospective evidence that the most effective treatment we have to offer patients at the moment is a combination of memantine and CHEI. This fits with the view that although amyloid and tau are the clear markers of AD, the development of dementia symptoms requires something more, and there are many other factors involved. Most of these involve synaptic loss for a variety of reasons, and manipulation of neurotransmitters will remain a corner stone of the multifactorial approach to managing this condition. It is unlikely we can cure what is fundamentally an organ failure related to aging and produced through a combination of genetics and lifestyle. However, hopefully with a combination of approaches including neurotransmitter modulation, disease-modifying agents, and addressing the inflammation and vascular risk factors, we should be able to allow patients to remain independent with a good quality of life without being disabled by their AD pathology.

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How Do We Use Symptomatic Drugs to Treat Dementia?

6

Takashi Kudo

6.1 Introduction

Symptomatic drugs for Alzheimer's disease (AD) target neurotransmitters.

The cholinergic nervous system is closely involved in memory and learning. The AD brain shows a conspicuous deficit of cholinergic nerve cells from the Meynert nucleus, which is combined with a reduction in acetylcholine synthesis. Therefore, the initial drug development strategy of pharmaceutical companies involved stimulating the acetylcholine system. They succeeded in developing cholinesterase (ChE) inhibitors acting as competitive inhibitors of acetylcholine degrading enzymes. This was an attempt to block the breakdown of acetylcholine, therefore increasing the amount of acetylcholine in the synaptic cleft. Drugs belonging to this category include donepezil, galantamine, and rivastigmine. In AD brains, excess excitation from glutamatergic neurons brings about neuronal death; therefore, memantine, an NMDA receptor antagonist, is also used in most clinical situations.

6.2 Characteristics of Symptomatic Drugs (Table 6.1)

6.2.1 Donepezil

Donepezil was the first ChE inhibitor to be used clinically. As a result, we now have a good deal of evidence, safety data, and clinical usage experience. Important characteristics of donepezil are that it (1) migrates effectively to the brain; (2) works selectively on acetylcholinesterase (AChE), has little effect on peripheral butyrylcholinesterase, and induces few GI side effects; and (3) has a long half-life (70–80 hours) making it suitable for once-daily administration. In addition, it is available in a variety of dosage forms: tablets, oral rapidly disintegrating tablets, and oral jelly tablets.

Donepezil usage normally starts with one 3-mg tablet daily, followed by observation for the onset of adverse reactions. If none are evident after 2 weeks, the dose

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Table 6.1 Symptomatic drugs for AD

	Donepezil	Rivastigmine (patch)	Galantamine	Memantine
	Cholinesterase inhibitors			NMDA receptor antagonist
Mechanism	Inhibitor to acetylcholinesterase	Inhibitor to acetylcholinesterase and butyrylcholinesterase	Inhibitor to acetylcholinesterase and elevator of acetylcholine receptor sensitivity	Noncompetitive voltage-dependent antagonist on NMDA receptor
Half-life(hr)	70–80	3.3 (18 mg patch)	5–7	60–80
Usage	3–10 mg	4.5–18 mg	8–24 mg (b.i.d.)	5–20 mg
Metabolism	CYP 2D6	Nonhepatic	CYP 2D6	Nonhepatic
	CYP 3A4		CYP 3A4	

is increased and maintained at 5 mg. For patients with moderate to advanced AD, the daily dose is raised to 10 mg. Adverse reactions include upper abdominal pain, loss of appetite, and vomiting. Special caution is required when prescribing high doses.

In 2010, the US FDA approved sustained-release 23-mg donepezil, and it has been indicated for moderate to advanced AD. It causes slightly more adverse reactions than the 10-mg dose, but significantly improves patients' cognitive symptoms. It is therefore likely that the dosage of donepezil used in clinical settings will increase to higher dosages.

Donepezil produces significant cognitive, behavioral, and global improvements in Lewy body dementia (DLB) patients. In Japan, its donepezil was expanded to DLB in 2014.

6.2.2 Galantamine

6.2.2.1 Galantamine's Allosteric Potentiating Ligand Action

Galantamine activates the acetylcholine system by the dual action of (1) elevating synaptic cleft acetylcholine levels via its cholinesterase inhibitor action and (2) elevating nicotinic acetylcholine receptor sensitivity via the allosteric potentiating ligand (APL) action. APL is an action whereby galantamine, an allosteric modulator, binds to allosteric sites different from acetylcholine- or agonist-binding active sites and induces conformational changes at the active sites of nicotinic acetylcholine receptors. This increases the action (affinity) of agonists, such as acetylcholine (Fig. 6.1).

Besides increasing signal transmission sensitivity, a drug with APL actions may have significant effects like (1) saturation of the active site, preventing overactivation ("ceiling effect"), (2) blockage of signal transmission unless a ligand already exists, (3) enhanced receptor selectivity for subtypes, and, lastly, (4) it is not liable to cause receptor desensitization or downregulation. Therefore, the drug could possibly enhance signal transmission safety.

6.2.2.2 Galantamine Activation of Nicotinic Acetylcholine Receptors

Because of galantamine's APL effects on nicotinic acetylcholine receptors, activation of the nicotinic acetylcholine receptor itself can be expected. When activating nicotinic acetylcholine receptors present in the presynaptic membrane, galantamine promotes the release of neurotransmitters such as norepinephrine, serotonin, glutamate, and γ-aminobutyric acid (GABA). Thus, it influences a person's psychiatric condition and is expected to have a parallel effect on the behavioral and psychological symptoms of dementia (BPSD).

Activation of nicotinic acetylcholine receptors may appear to bring about neuroprotective effects. In one study, a 13-week administration of galantamine resulted in significantly lower levels of tau protein in the cerebrospinal fluid (CSF), an indicator of nerve damage, than treatment with donepezil (Nordberg et al. 2009).

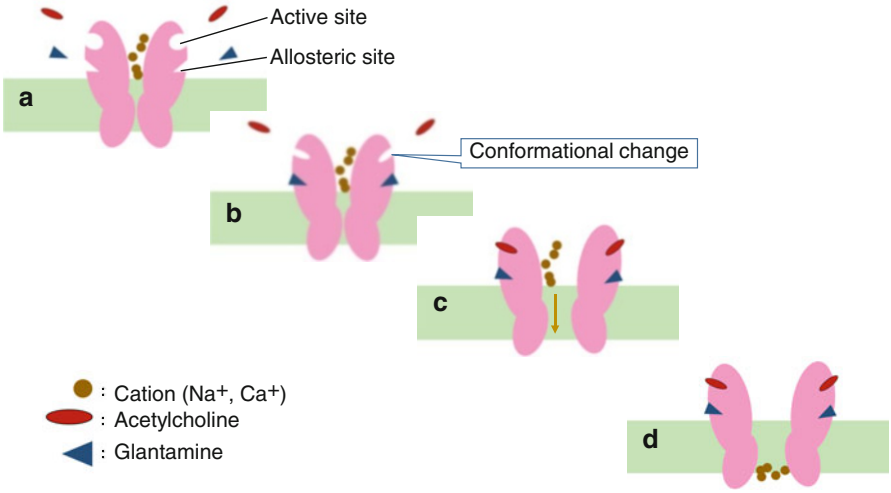

Fig. 6.1 Galantamine's allosteric potentiating ligand action. (**a**) Resting state of nicotinic acetylcholine receptor. (**b**) Glantamine binds to allosteric sites and induces conformational changes at active sites. (**c**) Acetylcholine favorably binds to active sites. (**d**) The channels opens to allow cations to pass through the membrane

Activation of nicotinic acetylcholine receptors also induces a rise in vasomotor reactivity; therefore, it is hoped to be applied to treat vascular dementia (Bär et al. 2007).

6.2.2.3 Galantamine Usage

Galantamine usage begins with a daily dose of 8 mg (b.i.d.) for mild to moderate AD. The dose is increased to 16 mg per day (b.i.d.) after 4 weeks. This may be further raised to 24 mg per day (12 mg b.i.d.), if symptoms require. Dosage increases should be done only after having administered the pre-change dose continuously for >4 weeks. This drug is also anticipated to have minimal adverse effects on peripheral butyrylcholinesterase and induces only minor gastrointestinal (GI), such as nausea and anorexia, and other adverse reactions.

6.2.3 Rivastigmine

6.2.3.1 Rivastigmine's Actions: Inhibition of AChE and Butyrylcholinesterase

Rivastigmine has effects on both AChE and butyrylcholinesterase. Most ChEs in the normal brain are AChE, with butyrylcholinesterase making up approximately 10 %. In the hippocampus, however, butyrylcholinesterase is present at relatively high levels. Although AChE is expressed in neurons, as AD advances its activity increasingly declines due to a deficit of neurons. On the other hand, because glial cells proliferate, butyrylcholinesterase activity shows a relative rise (Table 6.2)

Table 6.2 Acetyl- and butyrylcholinesterase activities in brain tissue (Perry et al. 1978)

	Age (years)	Postmortem delay (h)	Temporal cortex (μmole/h/mg protein)		Hippocampus (μ mole/h/mg protein)	
			AChE	BuChE	AChE	BuChE
Normal	73 ± 4	30 ± 7	2.49 ± 0.24	0.233 ± 0.024	3.46 ± 0.40	0.285 ± 0.049
Alzheimer	72 ± 4	36 ± 9	***1.67 ± 0.26	*0.327 ± 0.035	*2.15 ± 0.41	**0.471 ± 0.040

*, **, *** significantly different from the normal, p <0.05, 0.02, and 0.01, respectively

(Perry et al. 1978). The fact that rivastigmine has inhibitory actions on both enzymes works to its advantage.

6.2.3.2 Rivastigmine Transdermal Patch

The butyrylcholinesterase-inhibitory activity of rivastigmine is disadvantageous with regard to GI reactions compared with other ChE inhibitors. This is why capsule agents through the GI are refrained from using. A transdermal patch has recently been developed to lengthen the time for the drug to reach maximum blood concentration, since drug transfer to the bloodstream is slower from a patch compared to oral administration. The incidence of GI adverse reactions has therefore been reduced.

Rivastigmine usage begins with a daily dose of 4.5 mg. It is then increased by 4.5 mg every 4 week. For well-tolerated patients, it begins with 9.0 mg and 4 weeks later can be increased by 18 mg. An 18 mg patch can be applied to normal healthy skin on the back, upper arm, or chest daily as a maintenance dose and replaced every 24 hours. The dose may be increased (not to exceed 18 mg) or decreased in response to the patient's symptoms.

6.2.4 Memantine

6.2.4.1 Abnormalities of Glutamate NMDA Receptors in the AD Brain

In the AD brain, the concentration of glutamate rises continuously due to the actions of β-amyloid and other substances. They constantly act on NMDA receptors, causing excitotoxicity and synaptic noise that impairs calcium homeostasis. Glutamate excitotoxicity is one of the hypothesized mechanisms for neurodegeneration in AD.

With NMDA receptors, moreover, high concentrations of glutamate are released during long-term potentiation (LTP), causing temporary calcium influx and producing a signal. In the AD brain, however, the concentration of glutamate is chronically high, with synaptic noise occurring all the time. This LTP signal-masking noise is thought to lead to memory disturbances (Fig. 6.2).

6.2.4.2 Memantine Is a Noncompetitive Voltage-Dependent Antagonist

Memantine is a noncompetitive (open-channel) NMDA receptor antagonist with low to moderate affinity. Memantine's inhibitory action on NMDA receptor activity is dependent on membrane potential. During physiological neuronal excitation, glutamate is briefly released at high concentrations, elevating the postsynaptic

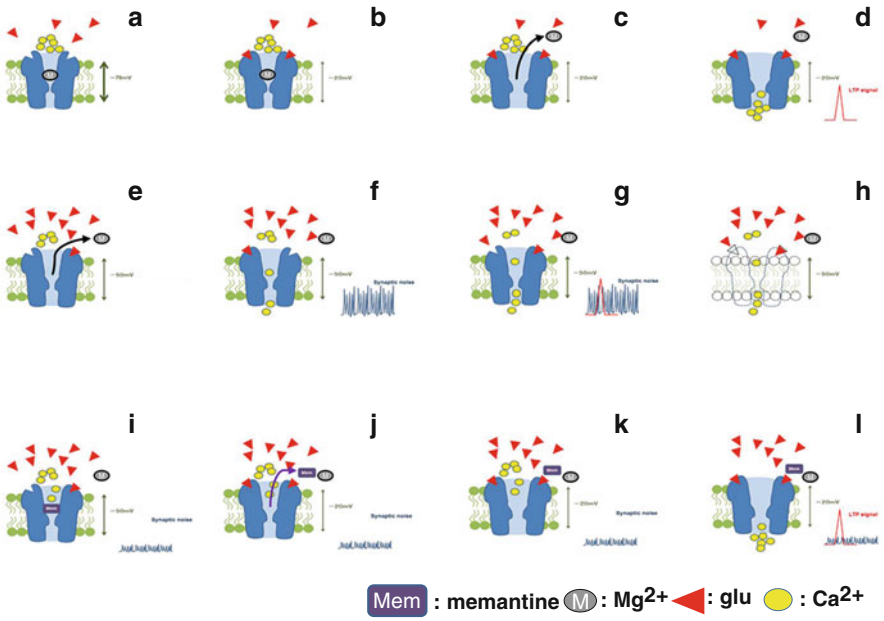

Fig. 6.2 Memantine is a noncompetitive voltage-dependent antagonist. (**a**) The ion channel is blocked by a magnesium (Mg^{2+}) under resting conditions. (**b**) When the NMDA receptor is activated by glutamate (glu), the postsynaptic neuron is depolarized (−70 mV → −20 mV). (**c**) Under the depolarization, magnesium leaves the ion channel. (**d**) The removal of magnesium causes a calcium influx, which is important for a long-term potentiation (LTP) signal. (**e**) In pathological conditions, such as in Alzheimer's disease, an increase of glutamate occurs in the synaptic craft resulting in continuous activation of NMDA receptors by lower concentrations of glutamate. The incomplete activation of the NMDA receptor depolarizes the postsynaptic neuron (−70 mV → −50 mV) and also releases magnesium from the ion channel. (**f**) The incomplete but continuous stimulation of NMDA receptor leads to an uncoordinated calcium influx, which enhances postsynaptic noise. (**g**) When a relevant LTP signal is presented, it is buried in the noise. This results in a deficit in cognitive function. (**h**) The stimulation of NMDA receptor with continuous calcium influx ultimately leads to damage of neurons. (**i**) By less pronounced voltage dependence of memantine (Mem) than magnesium, it can block the calcium influx under incomplete depolarization (−50 mV) of the postsynaptic neuron. Therefore memantine exerts a neuroprotective effect as well as suppresses synaptic noise. (**j**) However, under the strong depolarization causing LTP, memantine can dissociate from the ion channel due to its voltage dependency. (**k**) By a dissociation of memantine, the ion channel is ready for a surge of calcium influx. (**l**) The calcium influx generates LTP signal

membrane potential. Under these conditions, memantine easily dissociates from the NMDA receptor and does not impede physiological LTP. On the other hand, due to the continuous release of glutamate at relatively low concentrations under pathologic conditions, the membrane potential remains low in AD. Memantine is therefore believed to exert its neuroprotective effects as well as suppresses synaptic noise by inhibiting NMDA receptors. Memantine also allows the relevant physiological LTP signal to be detected. Both neuroprotection and symptomatic restoration of synaptic plasticity by memantine are provided by the same mechanism (Fig. 6.2).

6.2.4.3 Use of Memantine

Memantine usage should begin with a daily dose of 5 mg for moderate to advanced AD, with an increase by 5 mg per week. The maintenance dose is 20 mg orally once a day. Headache and confusion have been reported as adverse reactions to memantine.

6.2.4.4 Concomitant Therapy with ChE Inhibitors

In recent years, reports have shown greater effects of memantine when used in combination with ChE inhibitors. Memantine is also reportedly effective against excitement, agitation, and aggressiveness.

6.2.4.5 Effects on Behavioral and Psychological Symptoms of Dementia (BPSD)

The neurofibrillary tangles seen in AD brains are comprised of phosphorylated tau protein. The quantity of neurofibrillary tangles appearing are said to correlate with psychiatric symptoms (Faber et al. 2000). Memantine has been shown to inhibit the phosphorylation of tau protein (Li et al. 2004). Thus, memantine could have potential for the treatment of BPSD.

6.3 WFSBP Guidelines for the Treatment of Dementia

In 2011, the World Federation of Societies of Biological Psychiatry (WFSBP) released its "Guidelines for the Biological Treatment of AD and Other Dementias" (the Guidelines) (Ihl et al. 2011). It conducted a meta-analysis of clinical papers meeting set criteria and published the evidence on symptomatic drugs.

6.3.1 The Preventive Effects of Symptomatic Drugs

The WFSBP states that no data exist showing the preventive effects of donepezil, galantamine, rivastigmine, or memantine in patients aged below 70 and does not recommend administering these drugs for preventive purposes. It also states administration of such drugs cannot be recommended for mild cognitive impairment (MCI).

6.3.2 Indications for Symptomatic Drugs

The WFSBP states that no available drugs can be administered for curing or stopping the progression of AD, vascular, or other dementias. For symptomatic treatment of AD, the WFSBP recommends using donepezil, galantamine, and memantine, since they show some benefit, although for a limited period, in certain patients and do not cause serious adverse reactions (Grade 3: based on limited positive evidence from controlled studies). Although some countries have not declared indications for vascular dementia, the WFSBP recommends symptomatic drug use (Grade 3) for the time being. Rivastigmine has in some cases been recommended for dementia with Lewy

bodies (Grade 3), but there are no data showing other drugs' effects on dementia with Lewy bodies or frontotemporal dementia. However, the WFSBP states that these drugs could be potential therapeutic options for these types of dementia (Grade 4: based on evidence from uncontrolled studies or case reports/expert opinion).

6.3.3 Selection of Drugs and Their Dosage

The Guidelines state that drugs should be selected by taking the individual patient's symptoms into consideration, as well as the anticipated adverse reactions (Grade 4). Regarding the recommended usage amounts, the following daily doses are recommended: donepezil 10 mg, galantamine 24 mg, rivastigmine 12 mg (9.2 mg for a transdermal patch), and memantine 20 mg (Grade 3). The Guidelines state adverse reactions may be prevented at these doses (Grade 4).

6.3.4 Start and End of Drug Administration and Monitoring

The Guidelines state that drug administration should begin only after a diagnosis has been determined and therapeutic goals decided (Grade 4). The end of drug administration should be determined for each patient and must be done when serious adverse reactions appear or if requested by the patient, his/her family, caretaker(s), or official guardian (Grade 4). Patients should be carefully monitored for adverse reactions after starting a drug and for 6 weeks after adjusting the dose (Grade 4). Detailed observations are required for 3–6 months with the recommended dosages (Grade 4). If problems occur, the Guidelines call for a reexamination of diagnosis or consideration of the presence/absence of concomitant diseases. They recommend a reassessment in all patients at least every 6 months (Grade 4).

6.3.5 Concomitant Therapy

The Guidelines state concomitant therapy using symptomatic drugs may be considered, since there is a possibility that it creates synergistic effects (Grade 4).

6.4 Use of Different Symptomatic Drugs to Suit Different Situations Based on the Guidelines Released by Japan's Six Relevant Academic Societies

6.4.1 Guidelines Issued by Japan' Six Relevant Academic Societies

The Japanese Society of Neurology, the Japanese Society of Psychiatry and Neurology, the Japanese Society for Dementia Research, the Japanese Psychogeriatric Society, the Japan Geriatrics Society, and the Japanese Society of Neurological

Therapeutics collaborated to release the Guidelines for Dementia in 2010 (The Joint Committee for Formulating the Guidelines for Dementia 2010). A revision was made following the approval of three new drugs (galantamine, rivastigmine, and memantine), and a compact edition was published in 2012 (The Joint Committee for Formulating the Guidelines for Dementia 2012).

6.4.2 Policies on Using Symptomatic Drugs

Some people have opposed the use of drugs for symptomatic relief. However, placebo-controlled studies have confirmed all symptomatic drugs to be effective in delaying the progression of dementia for 1–2 years and even 5 years in some reports (Sumi and Shigeta 2013). One of these clinical studies reports the subjects in the placebo group, who were given the drug after a 1-year double-blinded test period, showed a greater progression of cognitive function decline than subjects who had started taking the drug from the beginning. This report suggests the importance of starting treatment early (Winblad et al. 2006). Besides their effect on cognitive function disorders, these drugs are confirmed to be effective for maintaining activities of daily living (ADL) and minimizing nursing care time. Although these effects may appear to be secondary, they have an extremely important significance to the patient, not to mention their family and/or caregiver(s). It is therefore imperative to explore methods of making full use of these drug effects and to maximize their benefits for dementia patients and families (Sumi and Shigeta 2013).

Symptomatic drugs cannot eliminate dementia symptoms or stop progression of the disease stage; they are not radical cure drugs. Although symptoms may temporarily improve, patients regress several years later to the point where drug therapy had begun and continue to worsen. Even though a patient may experience confusion less often or become more active in the short term as a result of initiating symptomatic drugs at an early stage, they eventually become more forgetful and the degree of nursing care increases. When this happens, patients, families, and even doctors may not be able to perceive treatment drug effects. In fact, as the degree of dementia advances, many patients discontinue drug therapy due to inefficacy (Umegaki et al. 2008). However, considering that the original effects of these drugs are to suppress the progression of disease, it is not favorable to discontinue them, at least at the mild to moderate stages of dementia (Sumi and Shigeta 2013).

It is extremely important to prescribe symptomatic drugs while also balancing the social resources available to patients and families. It is necessary to explore combinations with other non-drug treatment methods and support. With this as the premise, we must grasp the characteristics of each drug, understand the situation of patients and families, and select drugs that optimally elevate the quality of life for both patients and their families. We must pay full attention to detect whether the prescription of a drug is promoting peripheral symptoms, rather than improving them, and whether it is increasing the burden on the family. It is also important to

engineer methods to ensure the patient will take their drugs without fail (Oka and Mimura 2013).

6.4.3 Selection of Drugs

Past reports have shown no clear-cut differences in the effects of various ChE inhibitors on cognitive function disorders (Birks 2006; Hansen et al. 2008; Raina et al 2008). The Guidelines recommend matching the drug to the severity of the symptoms. Figure 6.3 shows the selection algorithm by disease stage and treatment drug featured in the Guidelines. It should be noted that this pertains only to core symptoms; therefore, the effect on BPSD should also be considered.

6.4.3.1 Severity

In Japan, galantamine and rivastigmine are indicated for mild to moderate AD, memantine for moderate to advanced AD, and donepezil for mild to advanced AD. Therefore, a ChE inhibitor would be selected for early-stage AD patients. The use of memantine can be considered as the disease progresses. The Guidelines recommend using functional assessment staging (FAST) and clinical dementia rating (CDR) to determine the disease stage/severity.

6.4.3.2 Period of Prescribing the Drugs

Some reports state cognitive functions are less labile if a patient has used ChE inhibitors at an early stage. Therefore, the use of such drugs should be considered as soon as possible after a diagnosis of AD. There is a possibility, however, that mild cognitive impairment (MCI) may include non-dementia pathologies, such as non-AD dementia and depression. Therefore, it is important that drug selection be done cautiously (Oka and Mimura 2013).

It is also necessary to recognize the option of switching drugs if symptoms change and, depending on circumstances, have the courage to temporarily discontinue drugs. Unless drugs have been discontinued because of severe adverse reactions, physicians must not rule out the possibility of resuming them. They should closely follow up with patients while checking the best time to restart therapy. Establishing objective criteria, such as assessing the effect of drugs and determining the timing of drug switches, is a continuous task (Oka and Mimura 2013).

Combination therapy with memantine and ChE inhibitors may be considered for moderate to severe cases. Although reports have expressed doubt on its efficacy (Howard et al. 2012), several recent reports suggest the efficacy of combined therapy (Atri et al. 2013; Gauthier and Molinuevo 2013). However, there is no consensus yet; various guidelines for dementia treatment currently approve of considering concomitant therapy for moderate to severe AD.

6.4.3.3 Adverse Reaction Countermeasures

GI symptoms are the most common side effect of all ChE inhibitors. These adverse reactions are most likely to develop at the start of administration and when the doses

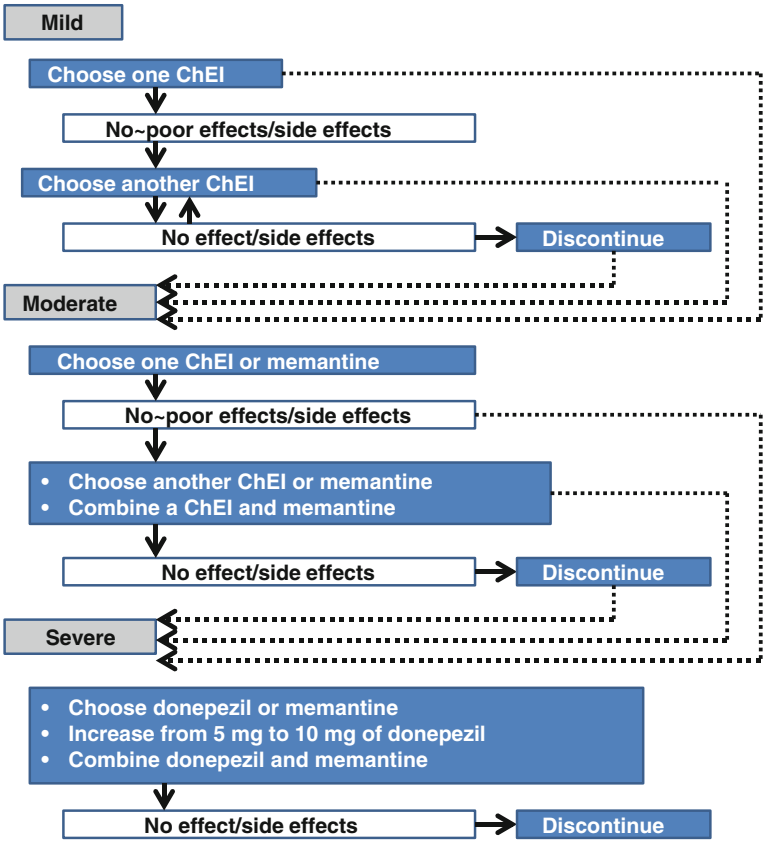

Fig. 6.3 The algorithm by disease stage and treatment drug featured in Guidelines for Dementia 2010, Compact Edition 2012. *ChEI* cholinesterase inhibitor

are increased. Therefore, the administration of all types of ChE inhibitors should begin with small doses and be increased gradually. In fact, in early-stage AD patients, GI symptoms are the main reason for discontinuing administration of ChE inhibitors (Umegaki et al. 2008). Some reports suggest that development of adverse reactions can be suppressed by increasing the dose at a much slower rate than that recommended on the package insert (Tsuno 2009). This also applies to memantine. Instead of increasing the dose every week from 5 to 20 mg/day, as recommended by the package insert, we may be able to alleviate adverse reactions by raising the dose more slowly (Sumi and Shigeta 2013). Concomitant use of proton pump inhibitors and gastric mucosal protection drugs is also recommended for improving GI symptoms (Sumi and Shigeta 2013). A switch to dermal patch agents could be considered to counter GI symptoms, since the blood concentration of the active agent does not rise sharply, therefore, being less liable to induce GI symptoms. However, patch agents are prone to inducing skin symptoms, such as redness and itchiness;

long-term use may require appropriate skincare and use of topical products (Oka and Mimura 2013).

Serious adverse reactions attributable to ChE inhibitors include A-V block and atrial fibrillation. Malaise and syncope may occur due to bradycardia. Nephropathy should also be considered when prescribing memantine (Oka and Mimura 2013).

When prescribing symptomatic drugs, it is important to be alert to the risk of complications and aware of past illnesses such as cardiac, intestinal, and renal diseases. Although no washout period is reportedly necessary when switching between symptomatic drugs, the type and extent of complications may necessitate return to initial doses, drug holidays, or slow dose increase (Oka and Mimura 2013).

With regard to use of ChE inhibitors, improvements in spontaneity and activity may lead to irritability, aggressive behavior, hyperkinesia, excitement/agitation, insomnia, and/or anxiety. In addition, while adverse reactions such as drowsiness associated with memantine work on impulsiveness and aggression, they also trigger a reduction in activity that can lead into somnolence and dizziness (Oka and Mimura 2013).

6.4.3.4 When to Discontinue Drugs

These symptomatic drugs are not radical treatment drugs. If symptoms become serious, deciding when to discontinue them is a difficult problem as it may result in the patient's family losing hope. Any resolution to discontinue medication, therefore, must be based on a broad view taking into account the family's thoughts and views.

6.4.3.5 Metabolism

Donepezil and galantamine are metabolized by CYP3A4 and 2D6. Care must be exercised when drugs affecting these enzymes (especially antidepressants) are used concomitantly.

On the other hand, rivastigmine is metabolized by esterase and is almost never affected by CYP. Since memantine is excreted 100 % through the kidneys, physicians should be aware that drug levels are significantly affected by renal function. If renal function is greatly impaired—specifically, if creatinine clearance is below 30 mL/min—the dose must be kept at a low level (Oka and Mimura 2013).

6.4.3.6 Patient Circumstances

Each drug has its unique characteristics in terms of dosing, dosage form, and price. All these need to be studied and adjusted to match the patient's circumstances, e.g., insight into his/her disease; swallowing function; presense/absense of complicatipns; etc. We recommend increasing the patient's dosing compliance while considering the preferences and intentions of the patient and his/her family.

Drugs should then be selected such that the patient can continue using them with minimal burden and stress (Oka and Mimura 2013).

6.4.3.7 Using ChE Inhibitors and Memantine to Suit Different Situations

If a reduction in spontaneity and motivation is present, it is advisable to use ChE inhibitors first. On the other hand, results of clinical trials have shown memantine to be effective against behavioral disorders (i.e., loitering, acting and behaving aimlessly, etc.) and aggressiveness (irritability, violence, etc.). Therefore, for moderate or severe cases, in which these symptoms are in the foreground, memantine is recommended as a first choice (Oka and Mimura 2013).

6.5 The Overviews of Symptomatic Drugs in AD Drug Guidelines

Table 6.3 shows the overviews of symptomatic drugs in AD drug guidelines which have been established, including the British Association for Psychopharmacology (BAP) Consensus Statement (Burn et al. 2006), European Federation of Neurological Societies (EFNS) (Hort et al. 2010), American Association of Family Physicians (AAFP) (Winslow et al. 2011), and National Institute for Health and Care Excellence (NICE) (NICE technology appraisal guidance 217 2011).

6.5.1 Use of Anti-dementia Drugs to Treat Diseases Other Than AD

The four currently available anti-dementia drugs have an indication for AD only, except donepezil, which is also indicated for Lewy body disease in Japan. Since a reduction in acetylcholine levels is also seen in vascular and frontotemporal dementia, existing ChE inhibitor drugs may be effective. At present, however, there is insufficient evidence to confirm this.

6.5.2 Future Tasks and Challenges

Guidelines for the treatment of dementia do not provide a detailed guide on drug use yet. Evidence would hopefully continue to accumulate and provide precise grounds for determining (1) the method for selecting various drugs, using different drugs to suit various situations, and using other drugs in combination and (2) the appropriate periods for starting and ending treatment while meeting patients' individual characteristics and background differences, including age of onset, morbidity period, duration of untreated period, biomarkers, and imaging data. Obtaining indications for diseases other than AD is also an urgent and important challenge.

Table 6.3 Symptomatic drugs in AD drug treatment guidelines

Guidelines	Year	Effects	Severity	Combination therapy	Treatments for diseases other than AD	Remarks
British Association of Psychopharmacology Consensus Statement (BAP)	2006	Type 1b evidence that AChE inhibitors do not reduce the risk of developing AD	Type1a evidence for AChE inhibitors for mild to moderate AD Type1b evidence for memantine for moderate to severe AD	Type 1b evidence for the effects adding memantine to AChE inhibitors	Type 1b evidence for AChE inhibitors for the treatment of Lewy body disease (particularly neuropsychiatric symptoms) Type 1b evidence for AChE inhibitors and memantine in treatment of cognitive impairment associated with vascular dementia	Type 1a evidence from meta-analysis of randomized controlled trials Type 1b evidence from at least one controlled trial
European Federation of Neurological Societies (EFNS)	2010	AChE inhibitors should not be used as treatments for those with MCI (Level A)	In patients with moderate to severe AD, treatment with memantine should be considered (Level A)	Endorses the use of memantine alone or in combination of AChE inhibitors especially when BPSD is present		Level A: according to the definitions given in the EFNS guidance
American Association of Family Physicians (AAFP)	2011	No notable differences in effectiveness among the various AChE inhibitors	AChE inhibitors are modestly effective in patients with mild to moderate AD	Combination therapy with an AChE inhibitors and memantine should be considered in patients with moderate to severe AD		

National Institute for Health and Care Excellence (NICE)	2011	AChE inhibitors and memantine treat the symptoms of Alzheimer's disease but do not slow the progression of the disease	AChE inhibitors are recommended as options for managing mild to moderate AD Memantine is recommended as an option for managing patients with moderate AD who cannot take AChE inhibitors and as an option for managing severe AD			
World Federation of Societies of Biological Psychiatry (WFSBP)	2011	No data exist showing the preventive effects of AChE inhibitors or memantine Administration of symptomatic drugs cannot be recommended for MCI No available drugs can be administered for curing or stopping the progression of AD, vascular, or other dementias		Concomitant therapy using symptomatic drugs may be considered (Grade 4)	Symptomatic drugs could be potential therapeutic options for vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (Grade 4)	Grade 4: evidence from uncontrolled studies or case reports/expert opinion
Guidelines issued by Japan' six relevant academic societies (in Japanese)	2012	No clear-cut differences in the effects of various AChE inhibitors on cognitive function disorders	AChE inhibitor would be selected for early-stage AD patients. The use of memantine can be considered as the disease progresses	Combination therapy with memantine and AChE inhibitors may be considered for moderate to severe cases		

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