Innovation in cholinergic enhancement for Alzheimer's Disease

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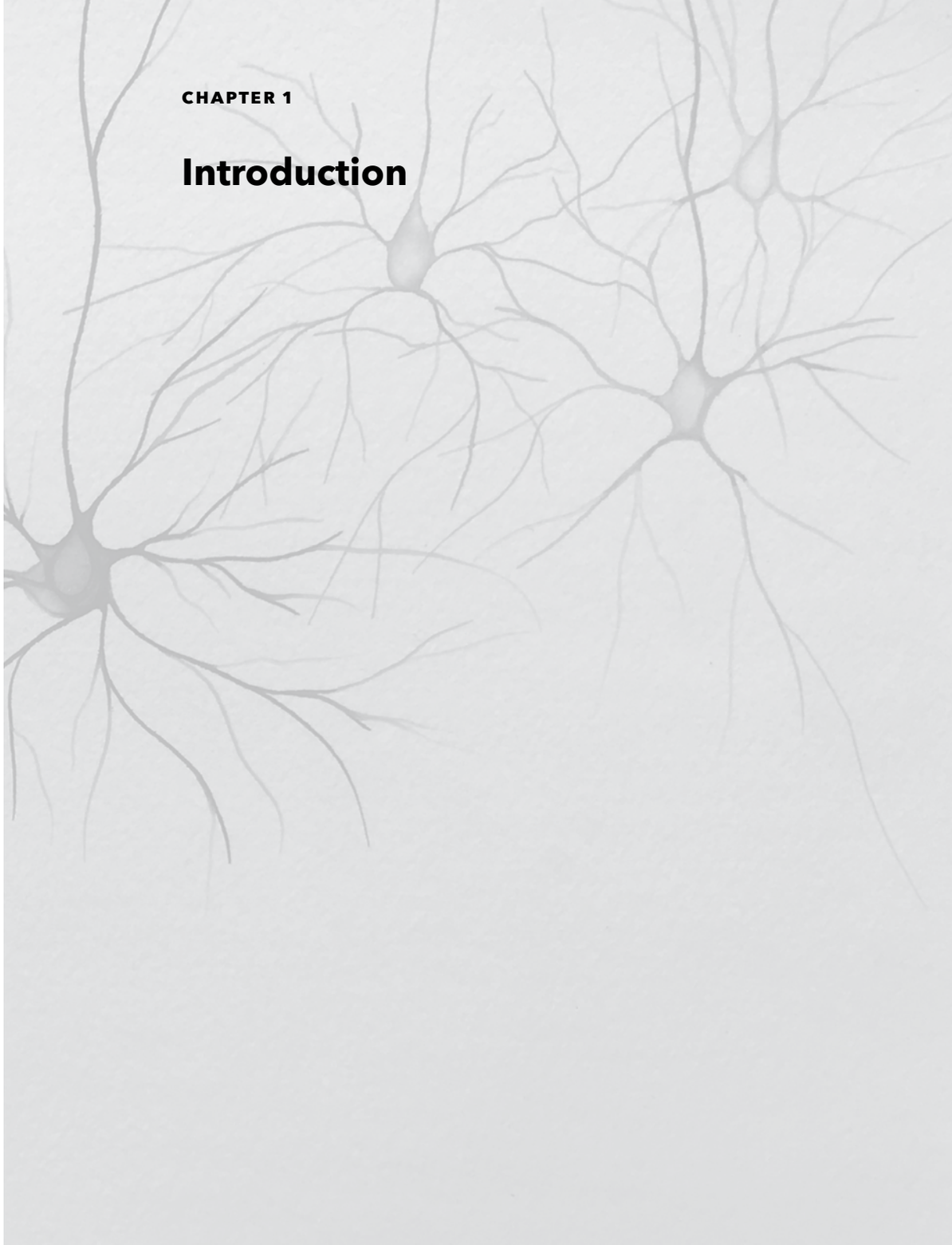
CHAPTER 1

Introduction



HISTORICAL CONTEXT

In 1906, the German psychiatrist Alois Alzheimer studied the case of Auguste D, a woman suffering from cognitive impairment in her early fifties. He described her symptoms in detail, including aphasia, apraxia, agnosia, disorientation, paranoia and memory deficits. After her death, he examined her brain and described the now well-known triad of neurofibrillary tangles, amyloid plaques and atrophy.[1,2] The combination of symptoms and pathological findings was later named Alzheimer's Disease (AD) by Emil Kraepelin, one of his colleagues. Although this was a new disease, it took over half a century before any progress was made in diagnosis and research. In the sixties and seventies, as a result of the success of the levodopa treatment for Parkinson's disease, it was discovered that certain neurotransmitter deficits were the central feature of a degenerative neurological disease and it became commonly assumed that a clearly defined neurochemical abnormality could also be identified in AD, which would provide the basis for the development of therapeutic interventions.[3] Post-mortem studies in the early seventies with brains of AD patients confirmed a substantial presynaptic cholinergic deficit, reduced choline uptake, reduced acetylcholine (ACh) release and loss of cholinergic neurons from the nucleus basalis of Meynert.[3] Additionally, other studies found a reduced choline acetyltransferase activity especially in those areas containing high density of neurofibrillary tangles, confirming a selective neurodegenerative process.[4] Clinical research in animals and humans confirmed that administration of anticholinergics induced memory loss and impairment in attention that were in some aspects comparable to the deficits occuring in aging.[5–8]

The positive effect of cholinesterase inhibitors like physostigmine on cognitive functioning supported this hypothesis.[7,9] All those discoveries resulted in the 'cholinergic deficit hypothesis' that at least some of the cognitive and behavioural symptoms of AD are explained by the lack of ACh, which was the dominant theory in AD in the early eighties.

Acetylcholine

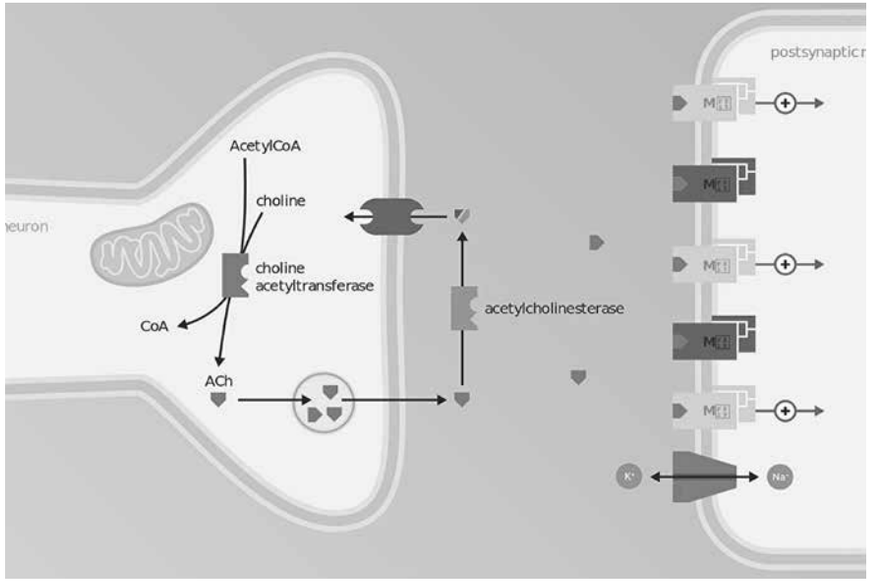
Acetylcholine is synthesized from choline and acetyl co-enzyme A by choline acetyltransferase. After depolarization of the presynaptic neuron, it is released in the synaptic cleft and binds to the postsynaptic receptors. To limit its action, acetylcholine is degraded by acetylcholinesterase in the synaptic cleft. The cholinergic system consists of the neurons using acetylcholine as neurotransmitter for transsynaptic communication. The highest density of these neurons is found in the basal forebrain (including the nucleus basalis of Meynert and the substantia innominata) and the brain stem, with a widespread projection to the cerebral cortex.[10] Cholinergic neurons can also be found in the peripheral nervous system and are crucial for neuromuscular signal transduction. The autonomic nervous system also contains many cholinergic neurons, influencing for example heart rate, blood pressure and bowel movements. Acetylcholine exerts its action by binding to the postsynaptic receptors, divided in two subtypes. The muscarinic AChRs in the central nervous system (CNS), especially the M1 subtype, are mainly located in the cerebral cortex, hippocampus, striatum, nucleus accumbens, dentate gyrus and brainstem and associated with memory, arousal and sleep.[11–15] Nicotinic AChRs are mostly found in the cerebral cortex, thalamus, hippocampus, dentate gyrus and striatum and associated with memory.[16,17]

There are several possible pharmacological approaches for stimulating the cholinergic system to accomplish a potential procognitive effect. To increase the level of ACh in the synaptic cleft, the break-down can be diminished by cholinesterase inhibitors. Another option is to stimulate the postsynaptic neuron with a direct AChR agonist. With these principals in mind, several compounds were developed to influence the cholinergic system.

In the second half of the eighties, several M1 AChR agonists were evaluated because of the high density of M1 AChRs in the hippocampus. In general, they had positive cognitive effects, but the cholinergic side effects overshadowed the benefits. This might have been due to a lack of selectivity leading to dominant peripheral cholinergic stimulation.[18] This strategy was therefore soon abandoned. The other approach, inhibiting ACh breakdown appeared more hopeful and several cholinesterase inhibitors were developed.[19–23] The cholinesterase inhibitor (CEI) tacrine was the first to acquire registration in 1995. The registration was supported by mitigating effects of tacrine on the scopolamine model of cognitive impairment in healthy volunteers.[24] However, this did not lead to widespread acceptance of the scopolamine model, or more generally of CNS testing, in healthy volunteers during the development of drugs for dementia. This may have been due to the disappointing effects of tacrine, which did not fulfill its huge expectations as a first-in-class anti-dementia drug. Soon after launch, tacrine was withdrawn because of limited clinical effects in combination with hepatotoxicity and gastrointestinal side effects (over 70% on the highest dose).[22,23] Consequently, other CEIs were developed, aiming to at least equal the clinical efficacy of tacrine, while inducing fewer side effects – but without using neuropharmacodynamic testing in healthy subjects. This led to donepezil and a few years later rivastigmine and galantamine entering the market. The pre-registration studies of these drugs were quite promising, indicating a positive effect on cognition in several

patient studies.[25,26] These drugs have also shown effects on cognitive tests in healthy (young and/or elderly) subjects, but this was only demonstrated late during development or after launch.[27] This thesis explores the possibility to use CNS pharmacodynamics much earlier during development of drugs in dementia, to provide proof of pharmacological activity and support dose selection. To understand the relevance of this approach, it is first important to summarize the more traditional development trajectories of these drugs.

FIGURE 1 Cholinergic synaps.



Rivastigmine

After careful evaluation in preclinical studies, further study of the new compound ENA 713 (rivastigmine) was carried forward to human subjects.[28] This started with a first in human study, investigating pharmacokinetics (PK), safety and tolerability of single doses up to 3 mg in 80 young healthy male subjects. These doses were well tolerated, but no information was obtained about cognitive function.[29] PK and safety studies were also performed in healthy elderly volunteers, although these data were never published.[28]

As a next step, safety, tolerability and efficacy were tested in a 13 week trial in 402 AD patients with doses of 2 and 3 mg of rivastigmine twice daily compared to placebo.[30] In the highest dose group, a beneficial effect on the Clinical Global Impression of Change (CGIC – a now rarely used impression of the change in overall clinical state of the patients) at week 13 was found for 43%, compared to 30% in the placebo group (p=0.05) and for DSS (Dementia Signs and Symptoms) at 7 and 13 weeks (p=0.005 and p=0.05 respectively). Adverse events (AEs) were generally mild, short, predominantly gastrointestinal and did not result in dose reduction or discontinuation. The low incidence of AEs and good tolerability suggested that higher dose of rivastigmine could be given. Since tolerability differences between patients and healthy volunteers had been previously reported after administration of CEIs, the possibility was considered that AD patients could tolerate doses of rivastigmine higher than 6 mg/day. This hypothesis was supported by a study assessing plasma PK and AChE inhibition in cerebrospinal fluid, indicating a much higher AChE inhibition centrally compared to the periphery.[31]

Consequently, a study was designed to investigate the maximum tolerated dose (MTD) in AD patients in order to test if higher doses could demonstrate greater efficacy in subsequent clinical trials. Fifty AD patients were randomized to receive 12 mg/day in two or three doses per day or placebo, for a 9-week dose escalation period followed by 1-week washout. In this study, the highest dose permitted was 12 mg/day, based on 50% of the no-toxic-effect level determined in animals. A MTD could not be established. Doses up to 12 mg/day were well tolerated, with the majority of patients experiencing only mild to moderate AEs. Surprisingly, but perhaps exemplary for the relatively uninformed protocols of the time measures of pharmacodynamics were not measured in this study.[32]

Next, a double-blind, randomized study in 114 AD patients was conducted to again assess adverse events and tolerability, this time combined with assessment of efficacy.[33] This study aimed to determine the MTD as well, while evaluating the tolerability of the same dose in a BID compared with a TID, but also to assess the efficacy of the individual MTD compared with placebo. In order to do that, patients received increasing doses of either rivastigmine BID, TID or placebo until they reached their MTD over the 10-week titration period, followed by an 8-week maintenance phase. The MTD was approximately 10 mg/day (both BID and TID); mild gastrointestinal complaints were the most frequent AEs. With respect to efficacy, a clear improvement in global function (CIBIC+), in cognition (ADAS-cog), and in activities of daily living (ADL) was seen. Nonetheless, the main goal of this study was to optimize dosage rather than testing efficacy. As a consequence, it has been criticized for that the sample size was too small and the duration of the trial too short.

These studies were followed by several double-blind, placebo-controlled clinical trials in AD patients, testing doses of 1-12 mg/day.[30,34–36] These studies showed a statistically significant improvements in the 6-12 mg/day group

compared with placebo on ADAS-cog, MMSE scales, CIBIC+ and ADL and led to the market approval of rivastigmine.

By providing more continuous delivery of drug into the bloodstream, it was expected that peak-dose fluctuations in drug plasma concentration would be reduced and, therefore, tolerability would be improved. After unsuccessfully developing an extended-release rivastigmine formulation Novartis started working on the development of a rivastigmine transdermal patch. The first study compared the efficacy, safety and tolerability of rivastigmine patches with capsules during 6 months in 1195 AD patients.[37,38] Patients were randomized to placebo, 10 cm² rivastigmine patch (delivering 9.5 mg/24 hours), 20 cm² rivastigmine patch (17.4 mg/24 hours), or 6 mg BID rivastigmine capsules (12 mg/day). The study established the 5 cm² patch as the recommended initial dose and the 10 cm² patch as the maintenance dose, becoming the first transdermal treatment for patients with mild-to-moderate AD in July 2007. As the study showed that 10 cm² of rivastigmine was safer but 20 cm² was more efficacious, Novartis planned to analyze the potential of a 15 cm² rivastigmine patch (delivering 13.3 mg/24 h) with the OPTIMA (OPtimizing Transdermal Exelon In Mild-to-moderate Alzheimer's Disease) study. OPTIMA demonstrated higher efficacy of the 15 cm² rivastigmine patch on functional outcomes compared to 10 cm², without compromising safety and tolerability.[39] Subsequently in 2012 the 15 cm² rivastigmine patch received approval by the FDA for the treatment of severe AD after the positive results of the ACTION (activities of daily living and cognition) study became public.[40] In this study, the 15 cm² patch demonstrated superior efficacy on ADL and cognition when compared to a 5 cm² patch for 24 weeks in patients with severe AD. The high-dose patch was generally well tolerated, with no unexpected safety concerns.[41] An open-label extension of the ACTION study showed greater decline in severe AD patients with delayed up-titration to high-dose 15 cm² patch compared to patients who received it since the beginning of the trial. In addition, no clinically relevant differences in safety and tolerability were observed.[42]

Donepezil

In 1983 Eisai Japan started with tacrine derivatives until they discovered a highly selective and reversible AChE inhibitor donepezil hydrochloride (E2020, Aricept®).[43,44] Donepezil was entered in clinical trial investigation in 1989. Phase I trials designed by Eisai used the erythrocyte membrane acetylcholinesterase (rbc-AChE) inhibition as measurement of pharmacodynamic (PD) activity. This was an improvement over rivastigmine, as an early evaluation of pharmacodynamics was done in Phase I, rather than just side effect incidence. A direct correlation was observed between plasma donepezil concentrations and rbc-AChE inhibition, with the obvious caveat that this may not be a direct measure of central inhibition. Later, phase II trials testing donepezil started to use several other clinical outcomes after a minimum of 8 weeks as a measurement of PD activity. Specifically, an open phase II study found that 9% of the patients taking 1 mg and 21% of those taking 2 mg improved their functioning, and 56% in the 1 mg group and 57% in the 2 mg group were slightly improved. Another phase II open trial found that in 22% of the cases the administration of donepezil was rated as more than useful, in 67% it was slightly useful, and there was no case were it was not useful at all.[45]

Phase III studies showed improvements in ADAS-cog, Clinician Interview-Based Impression of Change Plus (CIBIC+), and MMSE.[46]

Based on those pivotal phase III trials, in 1997 donepezil received marketing approval by the Food and Drug Administration (FDA) and was commercialized under the name of Aricept® by Eisai and Pfizer. Currently, donepezil (10 mg/day) is the most prescribed cholinesterase inhibitor worldwide.

After the FDA approval, a considerable number of studies have continued with this drug. Greenberg and Homma confirmed an improvement in cognition after 24 weeks of taking 5 mg/day of donepezil, and Krishnan and Burns confirmed this in patients taking 10 mg/day of donepezil for 24 weeks.[47–50]

Galantamine

Throughout the Caucasus Mountains, extracts from the snowdrop (*Galanthus spp*) have been used for hundreds of years to treat painful neurological conditions and poliomyelitis.[51] Once its synthetic production was established, galantamine was registered under the trade name Nivalin® and became commercially available in Bulgaria in the '50s for the treatment of post-poliomyelitis paralysis, myasthenia gravis and to reverse neuromuscular blockade in anesthesia.[52,53]

In the 1980s, researchers studying AD in Western Europe turned their attention to galantamine, because this does not only have beneficial effects on neuromuscular cholinergic function, but is also able to penetrate the blood–brain barrier.[51] For instance, galantamine injections reduced scopolamine-induced learning and memory deficits in rats, inhibited scopolamine-induced passive avoidance in rats, and improved spatial memory in mice with lesions to the nucleus basalis of Meynert.[54–56]

The 90s witnessed the clinical development of galantamine into a medication for AD. During this same period, the dual mechanism of action of galantamine was discovered, that is, galantamine inhibits AChE and at the same time potentiates nicotinic neurotransmission by allosteric modulation on nAChR.[57]

In vitro studies showed 50-fold selectivity for AChE, as opposed to cholinesterase confined to the peripheral circulation. In vivo administration of galantamine in a healthy volunteer and in a patient who underwent long-term treatment confirmed the high selectivity of galantamine for AChE.[58]

In 1989, the first modern phase I clinical study of galantamine was performed in 8 healthy volunteers.[59] The obtained pharmacokinetics suggest that the sc and oral Nivalin® formulations are bioequivalent. Thus, there seems to be no reason to prefer the sc instead of the oral route of administration. Additionally, the typical scheme of application at that moment used to begin with 2.5 mg/day, and it was eventually increased to 25-30 mg/day. However, an initial daily dose of 2.5 mg was too small to quickly reach biologically relevant steady state levels. Since this study showed that a single dose of 10 mg galantamine did not increase side effects, 10-15 mg as a loading daily dose at the very beginning of the galantamine treatment seemed preferable.

Three open pilot studies were published between 1989 and 1993.[60] The first study involved 10 AD patients receiving 30 mg/day of galantamine for 8 weeks. The results for CGIC, two psychometric tests and tolerability were promising, but in view of the low numbers understandably, statistically not significant for MMSE. In the second open pilot study, 18 AD patients received 30 mg/day galantamine. Although no statistically significant differences in neuropsychological tests were seen after 8 weeks, 6 patients with a favourable drug response continued for 13 to 16 months. This means that 30-60 % of these patients benefited from a sustained response to the drug. In the third trial, 19 AD patients received a low galantamine dose (30-40 mg/day) for 6 weeks and a high dose (45-60 mg/day) for 6 additional weeks, with a 3-week washout period between the two treatment phases. ADAS-cog and MMSE scores improved in the low dose regiment. Nevertheless, in this study the dropout rate was 37% due to adverse drug reactions. According to the Cochrane Review, there were some more early-phase clinical trials, although these are not publicly available.[61]

In 1993, the first galantamine study to employ a double-blind design was published.[61] The design of the study was the following: 3 weeks of starting washout period, followed by 3 weeks of single-blind 10 mg/day, then the dose was titrated up to 50 mg/day, and finally there were 10 weeks of double-blind maintenance phase. The 141 patients who completed the 3-week single-blind phase showed a dose-related improvement in ADAS-cog. Responders who had been randomized to continue in the treated group significantly improved in ADAS-cog, MMSE, SBT and CGIC, while placebo deteriorated. However, this study has been criticized for its too selective inclusion criteria, which makes the outcome reflect the potential of the drug, rather than its clinical efficacy.

In 1996, a placebo-controlled phase II trial studied the efficacy and safety of three doses of galantamine: 22.5, 30 and 40 mg/day. Patients treated with the 30 mg/day dose showed statistically significant improvements in the ADAS-cog scale.[62]

Phase III clinical trials studied the efficacy and safety of galantamine compared to placebo in patients with mild to moderate AD, providing evidence of efficacy and tolerability of the drug.[63–67] All those trials were published in the year the drug was launched or soon thereafter. Two different studies showed that after 6 months the cognitive function and clinical outcome of patients treated with both 24 and 32 mg/day of galantamine is maintained above baseline [63,65] with the same results after 3 months of treatment in another study.[66,67] Moreover, in one trial benefits were also seen in ADL and in a preserved functional performance.[67] In a 5-month trial was shown that patients receiving 16 and 24 mg/day of galantamine experienced a significant benefit in ADAS-cog and CIBIC+. Doses of 8 mg/day did not provide significant results. Since the 32 mg/day group did not generally provide significantly superior scores on cognition over the 24 mg/day dose but it did increase the AEs, daily 24 mg of galantamine was considered to be the optimal therapeutic dose.[64] All those trials were carried out for a maximum of 1 year, and longer powerful trials testing the long-term effect of galantamine in AD-treatment are still lacking.

CONCLUSION

The development of the cholinesterase inhibitors for Alzheimer's disease are a long and winding road of trials that are generally geared towards an effect on questionnaire-based outcome measurements. Whilst this is currently the only biomarker for clinical improvement in the disease, it is also relatively limited and difficult to assess. The human pharmacology of these medicines is easier to evaluate but does of course not necessarily relate to the clinical outcome. This is the dilemma for any future development of drugs for AD. If the early phase human pharmacology is ignored, the development will be done with relatively unsupported dose levels and a non-differentiating outcome measurement. The upper side of the dose range is then determined by an increase of subjective side effects. This has led to dosages that are registered but the approach is long and expensive and is difficult to use for new compounds. Alternatively more use can be made of early human pharmacology which is the approach that is practiced in the experiments in this thesis.

After the demise of tacrine, the development of all three currently registered CEIs started with traditional single and multiple ascending dose safety and

tolerability studies, without any cognitive outcome measures to assess efficacy in an early stage. So, the knowledge derived from these studies was about pharmacokinetics and side effects. Only during the development of donepezil, the effect on red blood cells was investigated as measure for pharmacological effects. Cognitive effects were first measured in phase III studies. In these large trials in AD patients, multiple doses compared to placebo were administered and efficacy was assessed after weeks to months, using clinical outcome measures, such as ADAS-cog, MMSE and clinician's global impression of change (CGIC). In some studies in patients with AD being treated with galantamine or donepezil, a computerized test battery was used at several time points between 1 and 52 weeks of treatment.[68,69] Thus, both the effective dose and efficacy on clinically relevant outcome measures were only studied in a later phase of clinical development, in heterogeneous patient groups over a relatively long treatment period. A different approach to development of neuropharmacological compounds is to combine the assessment of safety and tolerability, efficacy and dose finding in early phase I and II studies in healthy volunteers or small, well selected groups of patients. When sensitive, frequently conducted pharmacodynamic tests are used, in combination with pharmacokinetic measurements, proof of concept and an impression of the effective dose range can be acquired, even in small groups of healthy volunteers. This approach goes from the assumption that such early phase effects after a single dose may better reflect the pharmacological -and ultimately clinical effects than just dosing to a level where side effects become prohibitive. The value of such an approach has been shown on numerous occasions by us and others for an orexine receptor antagonist, a subunit selectieve GABA A agonist, neublastin in patients with sciatica and a compound reducing growth hormone release.[70-73]

Preview of this thesis

The central question of this thesis is if the integration of pharmacokinetics, CNS pharmacodynamics and clinical assessments in early phase drug development is feasible for drugs for Alzheimer's disease. AD affects global cognitive functioning and early studies – often in optimally functioning subjects may not be able to show improvement. The room for improvement is greater in patients (with a larger decline) but the potential for improvement may be less. Additionally, practical and ethical objections exist when groups of affected patients are included in early studies with inherent large burden for the cognitively impaired subject.

An obvious intermediate approach would be to induce a temporary state of cognitive dysfunction in subjects, preferably affecting the cholinergic system. For this purpose, the anti-muscarinic drug scopolamine is often used. However, scopolamine administration also induces a considerable level of sedation, which may obscure potential improvements induced by co-administration of a new procognitive compound. This thesis describes several examples of the above mentioned study designs and suggestions for further improvement.

Chapter 2 describes a study of the effects of several doses of the α7 nAChR partial agonist EVP-6124, alone and in combination with two doses of donepezil in healthy elderly subjects, receiving a scopolamine challenge prior to administration of EVP-6124 and/or donepezil.

Chapter 3 is an extensive exploration of another anticholinergic challenge model with the nAChR specific antagonist mecamylamine. Although this challenge model has been used before, its PD and PK characteristics were not well described and a detailed comparison with scopolamine was never done.

Chapter 4 delineates a PKPD model of mecamylamine and explains its use in study design.

Chapter 5 is a first in human trial with Gln-1062, a prodrug of the CEI galantamine, started on the standard starting dose of 10% of the level of no adverse effects (NOAEL) in animal studies. Since no PD effects were expected at the two lowest doses to be administered, these were given to healthy young male volunteers. In accordance with the pharmacodynamic approach that is central to this thesis, PK, PD and safety were measured.

Chapter 6 is a study in which we attempt to see if an early pharmacodynamic test battery after a single dose of galantamine predicts the response after 6 months. Such a study design could serve as an example to connect early phase pharmacodynamics to longer term clinical effects.

Chapter 7, a different approach to improve cognition was chosen. In this study, the histamine 3 receptor (H_3R) inverse agonist CEP-26401 was investigated. As histamine has an indirect effect on several neurotransmitter systems, including the cholinergic system, this might also be a target for procognitive medication. Based on previous studies with this compound, low doses were administered and its effects were compared to placebo, donepezil and modafinil.

REFERENCES

1 Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. Algemeine Zeitschrift für Psychiatr und Psych Medizin. 1907;64:146–8.
2 Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. Lancet. 1997 May 24;349(9064):1546–9.
3 Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. Vol. 66, J Neurol Neurosurg Psychiatry. 1999.
4 Davies P, Maloney AJF. Selective loss of central cholinergic neurons in Alzheimer's Disease. Lancet. 1976;308(8000):1403.
5 Bartus RT, Dean RL, Pontecorvo MJ, Flicker C. The Cholinergic Hypothesis: A Historical Overview, Current Perspective, and Future Directions. Ann New York Acad Sci. 1985;444:332–58.
6 Bartus RT. On neurodegenerative diseases, models, and treatment strategies: Lessons learned and lessons forgotten a generation following the cholinergic hypothesis. Vol. 163, Experimental Neurology. Academic Press Inc.; 2000. p. 495–529.
7 Drachman DA, Leavitt J, Ma C. Human Memory and the Cholinergic System A Relationship to Aging? Arch Neurol. 1974;30:113–21.
8 Bartus RT, Dean RL, Beer IB, Lippa AS. The Cholinergic Hypothesis of Geriatric Memory Dysfunction. Science (80-). 1982;217(4558):408–14.
9 Mohs C, Ph D, Davis BM, Johns CA, Horvath B, Davis L. Oral Physostygmine Treatment of Patients with Alzheimer's Disease. Am J Psychiatry. 1985;142:28–33.
10 Selden NR, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. Brain. 1998;121:2249–57.
11 Flynn DD, Reever CM, Ferrari-DiLeo G. Pharmacological strategies to selectively label and localize muscarinic receptor subtypes. Drug Dev Res. 1997;40(2):104–16.
12 Caulfield MP. Muscarinic Receptors-Characterization, coupling and function. Pharmacol Ther. 1993;58(3):319–79.
13 Pennartz CMA, Groenewegen HJ, Lopes da Silva FH. The nucleus accumbens as a complex of functionally distinct neuronal ensembles: An integration of behavioural, electrophysiological and anatomical data. Prog Neurobiol. 1994;42(6):719–61.
14 Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator. Neuron. 2012;76(1):116–29.
15 Vazquez J, Baghdoyan HA. Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. Am J Physiol - Regul Integr Comp Physiol. 2001;280(2 49-2).
16 Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: Behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology (Berl). 2006;184(3–4):523–39.
17 Paterson D, Nordberg A. Neuronal nicotinic receptors in the human brain. Prog Neurobiol. 2000;61(1):75–111.
18 McArthur RA, Gray J, Schreiber R. Cognitive effects of muscarinic M1 functional agonists in non-human primates and clinical trials. Curr Opin Investig Drugs. 2010;11(7):740–60.
19 Davis KL, Thai LJ, Elkan RG, Davis CS, Woolson RF, Gracon SI, et al. A Double-Blind, Placebo-Controlled Multicenter Study of Tacrine for Alzheimer's Disease. N Engl J Med. 1992;327(18):1253–8.
20 Murphy MF, Hardiman ST, Nash RJ, Huff FJ, Demkovich JJ, Dobson C, et al. Evaluation of HP 029 (velnacrine maleate) in Alzheimer's disease. Ann N Y Acad Sci. 1991;640:253–62.
21 Thal LJ, Ferguson JM, Mintzer J, Raskin A, Targum SD. A 24-week randomized trial of controlled-release physostigmine in patients with Alzheimer's disease. Neurology. 1999;52(6):1146–52.
22 Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan Ureno J. A Controlled Trial of Tacrine in Alzheimer's Disease. JAMA J Am Med Assoc. 1992;268(18):2523–9.
23 Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-Week Randomized Controlled Trial of High-Dose Tacrine in Patients With Alzheimer's Disease. JAMA J Am Med Assoc. 1994;271(13):985–91.
24 Wesnes KA, Simpson PM, White L, Pinker S, Jertz G, Murphy M, et al. Cholinesterase inhibition in the scopolamine model of dementia. Ann N Y Acad Sci. 1991;640:268–71.
25 Schneider LS, Mangialasche F, Andreasen N, Feldman H, Giacobini E, Jones R, et al. Clinical trials and late-stage drug development for Alzheimer's disease: An appraisal from 1984 to 2014. J Intern Med. 2014;275(3):251–83.
26 Birks J. Cholinesterase inhibitors for Alzheimer's disease (Review). Cochrane Database Syst Rev. 2006;(1).
27 Repantis D, Laisney O, Heuser I. Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: A systematic review. Vol. 61, Pharmacological Research. 2010. p. 473–81.
28 Polinsky RJ. Clinical pharmacology of rivastigmine: A new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. Clin Ther. 1998;20(4):634–47.
29 Enz A, Boddeke H, Gray J, Spiegel R. Pharmacologic and clinicopharmacologic properties of SDZ ENA 713, a centrally selective acetylcholinesterase inhibitor. Ann N Y Acad Sci. 1991;640:272–5.
30 Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: International randomised controlled trial. Br Med J. 1999;318(7184):633–40.
31 Kennedy JS, Polinsky RJ, Johnson B, Loosen P, Enz A, Laplanche R, et al. Preferential cerebrospinal fluid acetylcholinesterase inhibition by rivastigmine in humans. J Clin Psychopharmacol. 1999;19(6):513–21.
32 Sramek JJ, Anand R, Wardle TS, Irwin P, Hartman RD, Cutler NR. Safety/tolerability trial of SDZ ENA 713 in patients with probable Alzheimer's disease. Life Sci. 1996;58(15):1201–7.
33 Forette F, Anand R, Gharabawi G. Forette, Eur J Neur 1999, phase II dose finding rivastigmine in AD.pdf. Eur J Neurol. 1999;6:423–9.
34 Feldman HH, Lane R. Rivastigmine: A placebo controlled trial of twice daily and three times daily regimens in patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2007;78(10):1056–63.
35 Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. Int J Geriatr Psychiatry. 2004;19(3):243–9.
36 Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer ' s disease (Review) Rivastigmine for Alzheimer ' s disease. Cochrane Database Syst Rev. 2009;(2).
37 Winblad B, Cummings J, Andreasen N, Grossberg G, Onofrj M, Sadowsky C, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease - Rivastigmine patch versus capsule. Int J Geriatr Psychiatry. 2007;22(5):456–67.
38 Winblad B, Grossberg G, Fro L, Farlow M, Zechner S, Nagel J, et al. IDEAL: A 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology. 2007;69:S14–22.
39 Cummings J, Froelich L, Black SE, Bakchine S, Bellelli G, Molinuevo JL, et al. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm) in Alzheimer's disease. Dement Geriatr Cogn Disord. 2012;33(5):341–53.
40 Farlow MR, Cummings JL, Olin JT, Xiangyi Meng. Effects of oral rivastigmine on cognitive domains in mild-to-moderate Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2010;25(4):347–52.
41 Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M. A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe alzheimer's dementia. CNS Neurosci Ther. 2013;19(10):745–52.
42 Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Velting DM. A 24-Week, Open-Label Extension Study to Investigate the Long-term Safety, Tolerability, and Efficacy of 13.3 mg/24 h Rivastigmine Patch in Patients With Severe Alzheimer Disease. Alzheimer Dis Assoc Disord. 2015;29:110–6.
43 Sugimoto H, Iimura Y, Yamanishi Y, Yamatsu K. Synthesis and Structure-Activity Relationships of Acetylcholinesterase Inhibitors: 1-Benzyl-4-[(5,6-dimethoxy-l-oxoindan-2-yl)methyl] piperidine Hydrochloride and Related Compounds. Vol. 38, J. Med. Chem. 1996.
44 Kawakami Y, Inoue A, Kawai T, Wakita M, Sugimoto H, Hopfinger B' AJ. The Rationale for E2020 as a Potent Acetylcholinesterase Inhibitor. Vol. 4, Bioorganic & Medicinal Chemistry. 1996.
45 Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2018;(6).
46 Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease: A 15-week, double-blind, placebo-controlled study. Arch Intern Med. 1998;158(9):1021–31.
47 Greenberg SM, Tennis MK, Brown LB, Gomez-Isla T, Hayden DL, Schoenfeld DA, et al. Donepezil Therapy in Clinical Practice. Arch Neurol. 2000;57(1):94.
48 Homma A, Takeda M, Imai Y, Udaka F, Hasegawa K, Kameyama M, et al. Clinical Efficacy and Safety of Donepezil on Cognitive and Global Function in Patients with Alzheimer's Disease. Dement Geriatr Cogn Disord. 2000;11:299–313.
49 Krishnan KRR, Charles HC, Doraiswamy PM, Mintzer J, Weisler R, Yu X, et al. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. Am J Psychiatry. 2003;160(11):2003–11.
50 Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Möller H-J, et al. The Effects of Donepezil in Alzheimer's Disease - Results from a Multinational Trial 1. Dement Geriatr Cogn Disord. 1999;10:237–44.
51 Heinrich M, Teoh HL. Galanthamine from snowdrop - The development of a modern drug against Alzheimer's disease from local Caucasian knowledge. Vol. 92, Journal of Ethnopharmacology. 2004. p. 147–62.
52 Plaitakis A, Duvoisin RC. Homer's Moly Identified as Galanthus nivalis L.: Physiologic Antidote to Stramonion Poisoning. Clin Neuropharmacol. 1983;6(1):1–5.
53 Wislicki L. Nivalin (Galanthamine Hydrobromide), an additional decurarizing agent. Some introductory observations. Brit J Anaesth. 1967;39:963–8.
54 Fishkin RJ, Ince ES, Carlezon WA, Dunn RW. D-Cycloserine Attenuates Scopolamine-Induced Learning and Memory Deficits in Rats. Behav Neural Biol. 1993;59(2):150–7.
55 Chopin P, Briley M. Effects of four non-cholinergic cognitive enhancers in comparison with tacrine and galanthamine on scopolamine-induced amnesia in rats. Psychopharmacology (Berl). 1992;106(1):26–30.
56 Sweeney JE, Puttfarcken PS, Coyle JT. Galanthamine, an acetylcholinesterase inhibitor: A time course of the effects on performance and neurochemical parameters in mice. Pharmacol Biochem Behav. 1989;34(1):129–37.
57 Pereira EFR, Reinhardt-Maelicke S, Schrattenholz A, Maelicke A, Albuquerque EX. Identification and functional characterization of a new agonist site on nicotinic acetylcholine receptors of cultured hippocampal neurons. J Pharmacol Exp Ther. 1993;265(3):1474–91.
58 Thomsen T, Kewitz H. Selective inhibition of human acetylcholinesterase by galanthamine in vitro and in vivo. Life Sci. 1990;46(21):1553–8.
59 Mihailova D, I. Y, Zhikova Z, Tencheva J, Jovovich V. Pharmacokinetics of Galanthamine Hydrobromide after Single Subcutaneous and Oral Dosage in Humans. Pharmacology. 1989;39:50–8.
60 Rainer M. Galanthamine in Alzheimer's Disease. A New Alternative to Tacrine? CNS Drugs. 1997;7(2):89–97.
61 Olin JT, Schneider L. Galantamine for Alzheimer ' s disease (Review). Cochrane Database Syst Rev. 2002;(3).
62 Wilcock G, Wilkinson D. Galanthamine Hydrobromide - Interim Results of a Group Comparative, Placebo Controlled, Study of Efficacy and Safety in Patients with a Diagnosis of Senile Dementia of the Alzhemier's Type. Neurobiol Aging. 1996;17(4):S144.
63 Raskind MA, Peskind ER, Wessel T. Galantamine in AD : A 6-month randomized, placebo-controlled trial with a 6-month extension. 2000;54:2261–8.
64 Tariot PN, Solomon ; P R, Morris ; J C, Kershaw ; P, Lilienfeld ; S. A 5-month, randomized, placebo-controlled trial of galantamine in AD. Neurology. 2000;54:2269–76.
65 Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Br Med J. 2000;321(7274):1445–9.
66 Wilkinson D, Murray J. Galantamine: A randomized, double-blind, dose comparison in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2001;16(9):852–7.
67 Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: A randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2001;71(5):589–95.
68 Galvin JE, Cornblatt B, Newhouse P, Ancoli-Israel S, Wesnes K, David Williamson J, et al. Effects of Galantamine on Measures of Attention Results From 2 Clinical Trials in Alzheimer Disease Patients With Comparisons to Donepezil. Alzheimer Dis Assoc Disord. 2008;22(1):30–8.
69 Vellas B, Cunha L, Gertz HJ, De Deyn PP, Wesnes K, Hammond G, et al. Early onset effects of galantamine treatment on attention in patients with Alzheimer's disease. Curr Med Res Opin. 2005 Sep;21(9):1423–9.
70 Hoever P, De Haas S, Winkler J, Schoemaker RC, Chiossi E, Van Gerven J, et al. Orexin receptor antagonism, a new sleep-promoting paradigm: An ascending single-dose study with almorexant. Clin Pharmacol Ther. 2010;87(5):593–600.
71 Chen X, Jacobs G, De Kam ML, Jaeger J, Lappalainen J, Maruff P, et al. AZD6280, a novel partial γ-aminobutyric acid a receptor modulator, demonstrates a pharmacodynamically selective effect profile in healthy male volunteers. J Clin Psychopharmacol. 2015;35(1):22–33.
72 Okkerse P, Hay JL, Versage E, Tang Y, Galluppi G, Ravina B, et al. Pharmacokinetics and pharmacodynamics of multiple doses of BG00010, a neurotrophic factor with anti-hyperalgesic effects, in patients with sciatica. Br J Clin Pharmacol. 2016;108–17.
73 De Boon WMI, Van Esdonk MJ, Stuurman FE, Biermasz NR, Pons L, Paty I, et al. A Novel Somatostatin-Dopamine Chimera (BIM23B065) Reduced GH Secretion in a First-in-Human Clinical Trial. J Clin Endocrinol Metab. 2018;104(3):883–91.