Lessons Learned from Major Clinical Trials Conducted Over the Past Decades

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6.1 INTRODUCTION

In 2007 we celebrated 100 years of publications in Alzheimer’s disease (AD) research [1]. Alois Alzheimer, working in clinical psychiatry and neuropathology, linked cognitive decline with amyloid plaques and neurofibrillary tangles. Over this past century, extensive knowledge about the disease and its underlying pathophysiology has been accumulated [2]. A major therapeutic breakthrough was triggered by the findings of Drachman and Leavitt [3]. They observed that scopolamine-induced cognitive decline was similar to cognitive decline associated with aging. Together with the observation that AD is characterized by the degeneration and loss of cholinergic neurons in the nucleus basalis Meynert, located within the substantia innominata at the ventral surface of the basal forebrain [4], this ultimately led to the development of the symptomatic cholinergic drugs, with the first one being tacrine, marketed in 1991, and other better-tolerated ones to follow.

Improved biochemical analysis led to the determination of the molecular nature of amyloid plaques and neurofibrillary tangles and established the role of A-beta peptides and tau proteins [5]. In the mid 1990s, an additional major breakthrough was related to the linkage between decreased A-beta 42 levels and increased tau levels in cerebrospinal fluid (CSF) and clinical diagnosis of AD [6]. A small number of patients
suffer from inherited AD, based on meanwhile well-defined mutations in one of three genes: APP (amyloid precursor protein), PSEN1 or PSEN2 (presenelin 1 and 2). All these mutations directly affect the generation of A-beta 42, by either altering the substrate (APP) or the protease that cleaves this substrate (PSEN, the catalytic component of gamma-secretase) [5].

Over the years, based on these findings, a valuable biomarker tool for early diagnosis was developed [7]. This biomarker was based on observations that the calculated ratio of phospho-tau to A-beta 42 was significantly increased in patients with AD. Tests provided high diagnostic accuracy in distinguishing patients with AD from healthy control subjects (sensitivity, 86%; specificity, 97%), subjects with non-AD dementias (sensitivity, 80%; specificity, 73%), and subjects with other neurological disorders (sensitivity, 80%; specificity, 89%).

After this relevant step forward, the scientific field felt it would only be a matter of a few more years to find even more effective and probably also disease-modifying compounds to treat AD. In addition, from 1990 to the end of 1999, the Library of Congress and the National Institute of Mental Health of the National Institutes of Health sponsored a unique interagency initiative to advance the goals set forth in a proclamation by President George Bush designating the 1990s as the “Decade of the Brain.”

After the publication of the pioneering work of Braak and Braak in 1991 [8], in coincidence with improved imaging techniques [9], the overall impression was that the pathophysiology of AD was unlikely to reveal any major secrets.

In contrast to this impression, since the introduction of the cholinesterase-inhibitors and memantine targeting NMDA receptors, incredibly, no new classes of drugs have made it to the market for the treatment of AD. According to a recent report by Pharmaceutical Research and Manufacturers of America (PhRMA) released in 2012 [10], between 1998 and 2011, 101 treatments were investigated but failed to ultimately reach patients, of which 17 projects with final clinical data that targeted A-beta [11]. The overall ratio of failure to success was 31 to 1 (Figure 6.1).

The negative projects include a wide variety of mechanisms of action:

1. Inhibition of A-beta aggregation by tramiprosate (Phase III with over 1,000 pts) and scyllo-inositole (Phase II with 353 pts).
2. A-beta antibodies: bapineuzumab (Phase III with over 2,000 pts) and solanezumab (Phase III with over 2,000 pts).
3. Inhibition of gamma-secretase by semagacestat (Phase III with over 3,000 pts) and avagacestat (Phase II with over 600 pts).
4. Modulation of gamma-secretase by (R)-flurbiprofen/tarenflurbil (Phase III with over 2,400 pts).
5. Inhibition of tau-pathology via GSK3b-inhibition; tideglusib in Phase II with over 300 pts.

Some of these programs and their potential reason for failure are described in more detail below.

According to the PhRMA report, the following potential reasons were identified:

1. Scientists still do not fully understand the underlying causes and mechanisms of the disease, particularly when trying to separate potential causes from effects of the disease.
2. The limited utility of current animal models of the disease is a huge barrier in preclinical testing of drug candidates and limits their predictive validity.
3. The absence of validated non-invasive biomarkers of disease activity and progression.

Additional reasons could be the following: [12]

1. Poor methodology of animal studies.
2. Use of models that do not accurately reflect human pathogenesis.
3. Neutral or non-significant animal studies are less likely to be published.
4. Treatment comes too late, when damage is irreparable.
5. In line with PhRMA explanation No. 1 above, D. Smith [13] sees the focus on a wrong target, i.e. we need to challenge the underlying hypothesis that the formation of amyloid-beta (A-beta) drives the
pathophysiology of AD—instead of just being a result of underlying disease progression, as a key reason for consistent failure.

Other reasons could be seen in the need to use doses that enter the central nervous system (CNS) or have relevant biological activity in CNS. The potentially good news comes in a second 2012 PhRMA report [14]. America’s biopharmaceutical companies currently have 93 medicines in development for AD and dementias—either in human clinical trials or awaiting US Food and Drug Administration (FDA) review. However, about one-third of these ongoing projects are either directly targeting A-beta or doing this indirectly through the gamma-secretase pathway. The majority of the remaining therapies represent a symptomatic approach, only. In view of the so far fairly disappointing results, the question is whether A-beta in fact is (still) a valid target for disease-modifying treatment approaches.

6.2 THE AMYLOID APPROACH

There were several approaches to reduce beta-amyloid in the brain:

1. Reduce hypercholesterolemia.
2. Limit the creation of beta-amyloid and plaques.
3. Induce anti-body response to A-beta 42 via vaccination with subsequent clearance of amyloid plaques.

There are some good arguments why A-beta is the correct target, e.g. the genetic forms of A-beta overproduction leading to AD pathology and dementia.

None of these approaches has yet survived clinical testing, mainly because of a lack of demonstrable efficacy. Thus, the question arises of whether clinical study protocol features such as subject selection criteria, the selected study design, outcome measures, or treatment duration account for this failure—or whether the underlying pathogenetic concepts are fundamentally wrong.

6.2.1 Reduce Hypercholesterolemia

The reduction of hypercholesterolemia was considered an applicable approach to address the underlying A-beta hypothesis because high total cholesterol blood levels are positively correlated with A-beta plaques in the brain. However, there is only limited evidence that cholesterol is connected to A-beta cerebrospinal fluid (CSF) levels. The study by Simons et al. [15] is the only one to find simvastatin significantly decreased A-beta-40 levels in the CSF of patients with mild AD. The Rotterdam...
epidemiologic study indicated that the use of statins was associated with a reduced risk of AD [16].

Lesser et al. [17] found that nursing home residents with AD pathology (Consortium to Establish a Registry for Alzheimer’s Disease, CERAD) had significantly higher total serum cholesterol (TC) and low-density cholesterol (LDL) than residents without AD pathology. This was later confirmed in larger population studies, additionally showing that increasing certainty of AD (CERAD-based) [18] and increasing counts of neuritic plaques (NP), but no significant lipid neurofibrillary tangles (NF) correlations, were significantly associated with higher levels of TC and LDL.

This was confirmed recently in a series of 147 autopsies performed between 1998 and 2003 on residents in Hisayama town, Japan (76 men and 71 women), who underwent clinical examinations in 1988. Lipid profiles, such as TC, triglycerides, and high-density lipoprotein cholesterol (HDLC), were measured in 1988. Adjusted means of TC, LDLC, TC/H DLC, LDLC/H DLC, and non-HDLC (defined as TC–HDLC) were significantly higher in subjects with neuritic plaques (NPs), even in sparse to moderate stages (CERAD = 1 or 2), compared with subjects without NPs in multivariate models including ApoE4 carrier and other confounding factors [19].

In two rather small studies with 400–600 subjects, simvastatin and atorvastatin were assessed over an average of 18 months [20,21]. None of the primary and secondary endpoints showed significant improvements, though one cannot rule out that this was also due to the low statistical power of the study.

This model was also tested in the larger PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study; 5,804 patients aged 70 to 82 years without pre-existing dementia, but with a vascular risk factor such as vascular disease, nicotine-abuse, hypertonus or diabetes, were enrolled [22]. They were followed up over an average of 42 months with interim cognitive assessments at six different time points. No difference in cognitive decline at any of the cognitive domains was found in subjects treated with pravastatin compared with placebo (all p > 0.05). Pravastatin treatment in old age did not affect cognitive decline during a three-year follow-up period. However, pravastatin is passing the blood–brain barrier only to a very limited extent, which may also have contributed to this result [23]. Thus, what about the more targeted efforts to reduce the formation of A-beta?

An ongoing study with simvastatin, supported by the German ministry of research, now examines the potential to postpone conversion from mild cognitive impairment (MCI) to AD. However, the lack of efficacy of statins in modifying the course of AD casts a shadow on their ability
to modify the course in MCI. Although cognitive data from studies with statins in vascular disease suggest a primary preventive effect of statins on cognitive decline, the effects are uncertain due to the rather small degree of cognitive decline observed and a lack of operationalized AD diagnosis.

### 6.2.2 Limit or Prevent Plaque Formation

Tarenflurbil is a selective A-beta-lowering agent that demonstrated encouraging results on cognitive and functional outcomes among mildly affected patients in an earlier Phase II trial. It was tested in a multicenter, randomized, double-blind, placebo-controlled trial enrolling 1,684 patients with only mild AD [24]. Co-primary efficacy endpoints were changed from baseline to month 18 in total score of the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog, 80-point version) and the Alzheimer’s Disease Cooperative Studies-Activities of Daily Living (ADCS-ADL) scale. Tarenflurbil had no significant beneficial effect on the co-primary measures (difference tarenflurbil vs. placebo in change from baseline to endpoint), according to an intent-to-treat analysis. There were also no significant differences in the secondary outcome measures. The ADAS-Cog score decreased approximately by 7.1 points over 18 months in all groups (see Table 6.1). This could be interpreted as a failure of the underlying treatment approach. But, as in the previous example, the alternative explanation for this failure could be that only insufficient levels of tarenflurbil were able to cross the blood–brain barrier: Tarenflurbil only passes the blood–brain barrier at levels of 0.5–1.0% [25]. Tarenflurbil, however, had weak effects on amyloid levels in the brain and spinal fluid of patients with AD. But what if these biomarkers are a marker for an invalid target?

A related approach is based on the inhibition of beta or gamma-secretase—enzymes relevant to the formation of beta-amyloid in the brain; beta-secretase BACE is also under evaluation. Initial compounds had trouble reaching the brain or they got in but couldn’t stay, ousted in short order by P-glycoprotein. These early problems seem to be addressed. Lilly presented Phase I data on their BACE inhibitor LY2886721 in development for AD at the annual meeting of the American Academy of Neurology on March 18, 2013, but announced termination of Phase II in June 2013, due to liver toxicity of the drug. In December 2012 Merck initiated a Phase II/III clinical trial of its AD drug MK-8931 (Merck company communication).

Cleavage of APP, first by beta-secretase and then by gamma-secretase, fuels production of several brain A-beta peptides, including the highly amyloidgenic isoform A-beta 42. Gamma-secretase inhibitors may
6.2 THE AMYLOID APPROACH

decrease production of amyloid and potentially modify the progression of AD.

In one such study with Lilly’s gamma-secretase inhibitor, semagacestat, the clinical outcome was even worse under active treatment, compared with placebo. Development was stopped in 2010, after a pre-planned interim analysis of two Phase III trials for patients with mild to moderate AD showed that cognition and activities of daily living worsened in patients treated with semagacestat compared with those on placebo. That gave rise to the idea that beta-amyloid formation may be a result of AD progression or potentially even an attempted repair mechanism [26].

A comparable finding was seen for another investigational gamma-secretase inhibitor, avagacestat. In a Phase II dose-finding trial, trends for cognitive worsening were observed for patients on the two higher doses (100mg and 125mg daily) on the ADAS-Cog. Bristol-Myers Squibb planned for a new study to enroll patients in stages where clinical signs and symptoms of dementia are not yet evident, with patients identified based on biomarker evidence of AD. This pre-dementia study was planned to examine avagacestat dosed at 50mg/day for two years but was terminated in December 2012, due to lack of biologic effect at the lower dose (BMS company communication). This project could have helped to answer the question of whether A-beta is the right target, provided treatment is initiated at the right time, in early pre-symptomatic stages, or whether the timing is irrelevant because the treatment target is wrong.

<table>
<thead>
<tr>
<th>TABLE 6.1</th>
<th>Typical Example of the Summary of Primary Endpoint Results in Recent Studies with a Disease-Modifying Agent Targeting A-beta: Mean (SD) Change from Baseline in the Co-primary Endpoints in the Intention-to-Treat Population [24]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 Months</td>
</tr>
<tr>
<td><strong>ADAS-Cog</strong></td>
<td></td>
</tr>
<tr>
<td>Tarenflurbil (n = 786)</td>
<td>4.24 (7.99)</td>
</tr>
<tr>
<td>Placebo (n = 746)</td>
<td>4.28 (7.50)</td>
</tr>
<tr>
<td>Pvalue</td>
<td>.74</td>
</tr>
<tr>
<td><strong>ADCS-ADL</strong></td>
<td></td>
</tr>
<tr>
<td>Tarenflurbil (n = 751)</td>
<td>−5.36 (10.18)</td>
</tr>
<tr>
<td>Placebo (n = 725)</td>
<td>−6.05 (10.72)</td>
</tr>
<tr>
<td>Pvalue</td>
<td>.19</td>
</tr>
</tbody>
</table>
6.2.3 Vaccination/Immunotherapy

Immunotherapy covers passive (antibody application) and active immunotherapy (vaccination strategies). Vaccination refers to giving a peptide fragment to induce active antibody production by the body (active immunotherapy).

Passive concepts: In the pivotal Phase III EXPEDITION studies in over 2,000 patients with Lilly’s lead compound, solanezumab (a monoclonal antibody that binds to soluble forms of beta amyloid), only a pre-specified sub-group analysis of patients with mild/early disease revealed a statistically significant benefit over placebo [27], with a 42% reduction in cognitive decline at 18 months.

The original analysis did not indicate any significant effects on both pre-defined primary endpoints, and this was confirmed in a second trial that involved patients with mild to moderate AD. A statistically significant difference between active drug and placebo was found neither on the ADAS-Cog nor on the ADCS-ADL scale.

A possible interpretation of these findings would be that a disease-modifying therapy that targets A-beta has to start very early in the disease progression, before any major brain damage occurs.

Bapineuzumab, a monoclonal antibody that targets beta-amyloid, comes with a very similar story: Results of biomarker sub-studies, included in the bapineuzumab trials, showed significant differences in the amount of amyloid in the brain and phospho-tau in CSF between patients with AD carrying the apolipoprotein E4 (ApoE4) genotype who received bapineuzumab and those taking placebo [28]. The results of two large Phase III randomized, double-blind trials of bapineuzumab (Johnson & Johnson and Pfizer Inc.) in patients with mild to moderate AD nonetheless showed that the treatment failed to meet co-primary clinical endpoints of change in cognitive and functional performance compared with placebo in ApoE4 carriers and non-carriers, respectively.

The new biomarker results can be interpreted in different ways, depending on one’s preconceived notions about the amyloid cascade hypothesis: The findings demonstrate that the antibodies reach and remove amyloid in the brain, as shown on the Amyloid-PET scans [29], and that there was less of a downstream effect from amyloid deposition, as seen from measures of phospho-tau in the CSF.

For a believer in the A-beta hypothesis, the lack of clinical effects could still be explained by a start that comes too late to have a significant impact of pathophysiological cascade of events.

With gantenerumab, a monoclonal antibody that binds to all forms of aggregated beta amyloid, Roche is also targeting early stages of the disease. Gantenerumab is currently being tested in an international Phase II/III trial in prodromal AD. Also for this compound, earlier studies
resulted in a dose-dependent reduction in brain amyloid level, possibly through an effector cell-mediated mechanism of action [30].

Rachelle S. Doody, MD, PhD, Director of the Alzheimer’s Disease and Memory Disorders Center at Baylor College of Medicine in Houston, Texas, pointed out that [31] “…there are at least seven other antibody-related infusion treatments under development and in human stages of testing, and none of them have so far been proven to benefit patients clinically.”

6.2.3.1 Active Vaccination

A study led by the Karolinska Institute in Sweden reported, for the first time, positive effects of an active vaccine against AD with the new vaccine, CAD106 [32]. The treatment involves active immunization triggering the body’s immune defense against A-beta. In this second clinical trial on humans, the vaccine was modified to affect only the harmful beta-amyloid; 80% of the patients involved in the trials developed their own protective antibodies against A-beta without suffering any side effects over the three years of the study.

Some answers as to whether the described situation of negative or failed studies is due to a “wrong target or wrong timing” may come from the long-term results of a prematurely ended A-beta 42 active immunization study in AD. The study was stopped early for safety reasons with patients developing meningoencephalitis.

Of 372 patients treated in the initial Phase IIa study (300 active; 72 placebo), a total of 264 (71.0%) were contacted to determine interest in follow-up study participation [33]. 159 agreed to participate in the follow-up study (30 placebo; 129 treated with AN1792). Of the original 59 subjects who were classified in the Phase IIa study as antibody responders, 25 (42.4%) agreed to participate in the follow-up study compared with 30/72 (41.7%) of the placebo-treated patients.

The majority of patients enrolled in this follow-up study were taking concomitant acetylcholinesterase inhibitors or memantine. The proportion of patients taking concomitant medications was similar between antibody responders and placebo-treated patients. After approximately 4.6 years of follow-up, antibody responders demonstrated a 25.0% lower decline in activities of daily living as determined by the Disability and Dementia (DAD) scale compared with placebo-treated patients. Comparisons of cognitive function in this follow-up study may not be representative of the entire placebo-treated group, and may favor the assessment of placebo-treated patients who were less impaired and capable of undergoing cognitive testing. The neuropsychologic test battery (NTB) was attainable in only 10/30 placebo-treated patients (33.3%) and 13/25 antibody responders (52.0%). No significant differences were observed in the change from baseline for the overall NTB nine-component z-score between antibody responders and placebo-treated patients. The ADAS-Cog was attainable in 11/30 placebo-treated patients.
(36.7%) and 16/25 antibody responders (64.0%). No significant differences in ADAS-Cog score were observed between placebo-treated patients and antibody responders after approximately 4.6 years of follow-up.

In a six-year follow-up post vaccination in 80 subjects [34], including post-mortem analysis of subjects that underwent immunization to clear plaques from the brain, A-beta clearance did not prevent the progression of neurodegeneration and dementia. The authors claim that:

- presence of A-beta plaques might be necessary to initiate, but not to maintain, progressive neuro-degeneration […] Second […] the removal of plaques after AN1792 immunization could be a slow process […]. Third, […] immunization could fail to reduce the concentration of oligomeric A-beta and the concentration might even be increased during the active phase of disintegration of A-beta plaques. According to this view, aggregated A-beta in the form of plaques is harmless, or could even be protective […].

See also Figure 6.2.

### 6.3 ALTERNATIVE TARGETS

It therefore seems to be crucial to focus on targets other than A-beta, such as tau-protein. In AD, the brain contains two types of aggregates: intracellular
neurofibrillary tangles (tau protein) and extracellular senile or “amyloid” plaques consisting of the A-beta peptide, a cleavage product of the membrane protein APP [35].

Tau proteins are highly organized protein aggregates and are considered to be mediators of cellular toxicity and thus attract a great deal of attention from investigators. The last decade has witnessed a renaissance of interest in inhibitors of tau aggregation as potential disease-modifying drugs for AD and other “tauopathies” [36].

Tau, however, is an intracellular protein. Even though there are drugs under development to inhibit tau activation, these drugs need to be intra-cellulary active—with a risk of unexpected adverse reactions on brain cell metabolism [37].

So far, the situation with compounds that are targeted at tau protein is not much more promising: Tideglusib, an irreversible inhibitor of GSK-3 which inhibits tau protein phosphorylation in neuronal cultures and in pertaining transgenic mice models, showed disappointing results in Phase III studies.

Nonetheless, another innovative concept was linked to a drug development focused on tau: The patient recruitment company Medici Global developed a Facebook page to help those living with AD and to help bring new medicines to market [11], by attempting to promote a Phase III study in 21 countries with LMTX, a compound which shall dissolve tangles.

As disease-modifying drugs are still an option but expensive to develop, what else can be done?

6.4 ALTERNATIVE APPROACHES AND STUDY DESIGNS

In case one favors a treatment approach based on the concept of “the earlier the better,” the question arises as to “how early should early be?” When considering this approach, one needs, according to Selkoe [38], to differentiate between primary and secondary prevention on the one hand and early symptomatic treatment on the other (Figure 6.3). Such outcome studies would need to follow non-symptomatic patients at risk of developing AD over several years. The hypothesis is to lower conversion into AD with active therapy.

The design of such projects would in principle follow recently published studies in vascular primary and secondary prevention (e.g., primary prevention of stroke in patients with ventricular fibrillation) [39]. Such projects may only be feasible under certain conditions:

- They require a well-defined and pre-selected patient population at the highest possible risk of conversion to AD in the not too distant future.
FIGURE 6.3 Aligning potential disease-modifying agents for AD with the course of the disease. Boxes on the left: clinical trial categories dependent on the stage of AD. “X” in bottom left box: trials in moderate AD not recommended. “X” in second-bottom box on left: trials in mild AD recommended with caution. Boxes on the right: speculative stages in the long pre-symptomatic and symptomatic phases of AD in a hypothetical individual who undergoes A-beta build-up. Figure adapted from [38].
● Therapy needs to be well tolerated to be acceptable for a still healthy population.
● Therapy needs to be easy to use (e.g., once daily oral application) to allow adherence to therapy in a preventive setting over months and years.
● Assessments need to be most non-invasive to pass IEC/IRB approval.

This concept was already agreed on in 2006 [40].

An in-depth discussion about the potential use of markers to “enrich” the population enrolled for follow-up can be found in [41].

The dilemma is that there is no agreement on what are the most sensitive and specific biomarkers that may predict later AD onset—and that biomarkers from CSF require an invasive lumbar puncture.

Non-invasive biomarkers would be beneficial in spotting those patients at highest risk for developing AD. In a longitudinal evaluation of the available data in “Alzheimer’s disease neuroimaging initiative” (ADNI), Gomar et al. [42] studied patients with mild cognitive impairment who converted to AD (n = 116) and those who did not convert (n = 204) within a two-year period. They determined the predictive utility of 25 variables from all classes of markers, biomarkers, and risk factors in a series of logistic regression models and effect size analyses. Various types of markers were included, such as regional brain volumes, CSF measures of pathological A-beta 42 and total tau, cognitive measures, and individual risk factors. The results indicated that cognitive markers at baseline were more robust predictors of conversion than most biomarkers. A similar proof for cognitive markers was provided by the German Competence Network Dementia in a prospective study of subjects with MCI [43].

Another possible answer could be provided by performing such studies in AD patients who suffer from a hereditary variant of AD (dominantly inherited AD). Autosomal dominant AD follows a different time course with disease onset around the age of 48 years in patients with the most prevalent presenilin mutations, but has similar neuropathological findings and symptomatology.

The Dominantly Inherited Alzheimer Network (DIAN) [44] tries to address this concept by currently enrolling and thoroughly evaluating about 400 such patients in the USA, Australia, and Europe. In the case of a successful outcome, this study could be the basis for proof-of-concept studies in a well-defined and pre-selected patient population.

Other strategies to use enriched samples with people with a high genetic risk are to evaluate new treatments in cohorts of ApoE4-positive persons with further genetic markers [45]. This means that identifying people at risk of developing the disease may provide a more promising
population for future studies. They may get identified by a genetic predisposition or by measuring biomarkers, such as the recently reported CSF measurement of a mix of A-beta 1–42 and phosphorylated tau protein.

In an attempt to find early pre-dementia patients for its gamma-secretase inhibitor avagacestat study, BMS screened 1,350 potential subjects. Only 550 of those met the criteria of MCI, and of those, only 48% met the biomarker criteria in CSF after lumbar puncture, creating an overall screen failure rate of 81% [46].

The situation described raises a very practical question: which company would be willing to identify, enroll, and follow up over nearly a decade thousands of subjects at an even earlier stage of the disease—with the need to screen many more subjects?

The FDA tried to address this dilemma by providing new guidance for industry with a focus on early stages of the disease [47], which is also summarized in [48]. The main change is to accept cognitive endpoints only, since daily functioning may not yet be affected in early stages. The FDA is open to considering the argument that a positive biomarker result (generally included as a secondary outcome measure in a trial) in combination with a positive finding on a primary clinical outcome measure may support a claim of disease modification in AD. Until there is widespread evidence-based agreement in the research community that an effect on a particular biomarker is reasonably likely to predict clinical benefit, the FDA will not be in a position to consider an approval based on the use of a biomarker as a surrogate outcome measure in AD (at any stage of the illness).

A recent study added further doubt to the “need to treat early” concept. The symptomatic therapies donepezil and memantine showed positive effects at advanced stages of the disease; 295 patients with a Mini Mental status of 5–13 points (indicating progressed stage of the disease), and already on therapy with donepezil, were randomized to one of four treatment groups: continue donepezil therapy, end therapy, switch to memantine, and add memantine to donepezil. After one year of observation, patients statistically significantly benefited from active treatment [49]. If symptomatic therapy requiring neuronal and synaptic response is still effective in later stages of the disease, why should other therapies that also require a remaining “critical mass” of neurons not work at all in even earlier stages?

An alternative approach could thus be the re-evaluation of mechanisms identified as relevant for the therapy of AD prior to the era of disease-modifying research. The list of drugs used prior to the introduction of cholinergics is as long as the assumed modes of action of these compounds. Pyritinole, meclofenoxate, co-dergocrine, pentoxifylline, nimodipine, ginkgo biloba, naftidrofuryl, nicergoline, and memantine shall act via impact on
various neurotransmitters such as acetylcholine, norepinephrine, dopamine, glutamate, and serotonin (for details see [50]).

1. Activation of neuro-metabolism (e.g., by activation of hexokinase, glucose-6-phosphat dehydrogenase, cytochrom-c-reductase, adenylatkinase, and facilitation of oxygen-uptake.
2. Increase cerebral microcirculation.
3. Reduction of free radicals in the brain and of oxidative stress, e.g., activation of superoxiddismutase, gluthathionperoxidase, and gluthathionreductase.
4. Immunomodulation such as inhibition of tumor-necrosis-factor alpha (TNF-alpha).
5. Limit calcium load of (neuronal) cells.

Orion Pharma disclosed the results of a 100 pts Phase II proof-of-concept study with the new selective alpha 2C adrenoreceptor antagonist, ORM 12741, as add-on therapy to a cholinesterase inhibitor drug. After three months, the memory scores for those who received the placebo pill had worsened by 33%, whereas the scores improved by 4% for those who took the active drug at two dose levels [51]. Another potential target for new AD drugs was recently re-evaluated: The aluminum hypothesis of the 1980s got new support with the observation that ferritin molecules are not only found in unusually high concentration in AD brains, but that these ferritin molecules do not contain iron but on average contain 62% aluminum. Even though this is a small study of only 21 AD patients compared with 200 healthy subjects, the results may be the “missing link” to explain how neurotoxic aluminum can pass the blood–brain barrier and why high aluminum exposure can thus trigger neuronal death [52].

Once any of these potentially symptomatic and disease-modifying mechanisms manage to provide proof-of-concept, it would be best to apply more advanced drug-design methodologies such as the “Delayed-Start Study Design”, also called “Randomized-Start Design.” The FDA also supports this approach, saying:

We have not yet reached a conclusion that a comparison of the rate of change in key clinical efficacy parameters (based on slopes) between active treatment and control groups, using a standard parallel-arm study design, could provide the sole support for a claim of disease modification. A randomized-start or randomized-withdrawal trial design (with clinical outcome measures) appears to be a more convincing means of demonstrating such an effect. For ethical reasons, a randomized-start design would be most appropriate for use in AD [47].

In step 1 of this design, patients receive the assigned treatment (active or placebo) and are followed over an extended period of time; this allows the effects of the treatment on symptoms to be observed. In step 2, all
patients receive the active treatment, and the data obtained during this phase are used to evaluate the disease-modifying effects of the active drug [53]. This advanced design would allow the assessment of a symptomatic and a potential disease-modifying effect in one study. This design was only applied once with partial success in a related disorder; in Parkinson’s disease [54]. See also Figures 6.4–6.6.

These innovative study designs can be even further developed, up to a complete two-period design [55] (Figure 6.7).

### 6.5 CONCLUSIONS

A-beta and related targets have consistently showed negative results in Phase III studies in this first decade of the 21st century, after showing promising trends in Phase II. This could be due to three major reasons:

1. The wrong patient population was observed, e.g., therapy started too late in the progression of the disease.
2. The effects of these therapeutics on A-beta were not large enough (potentially because of too low doses) or did not target the most toxic species of A-beta.
3. A-beta is the wrong target.

All of the above reasons may be true. Which of these main alternatives is correct cannot be finally determined, yet. Since so far no pivotal study
targeting A-beta has shown clinical effects, it is fairly improbable that there is any true effect that so far could not have been demonstrated. The post-hoc identification of some trend in some less progressed disease is similar to trends observed in (also underpowered) Phase II studies and could also be explained by random fluctuations.

FIGURE 6.5  Real data from the rasagiline study: 1 mg/day dose arm. These results have a very similar shape as in the hypothetical concept displayed in Figure 6.2 above [47].

FIGURE 6.6  Real data from the rasagiline study: 2 mg/day dose arm. This is a result you would expect from a purely symptomatic therapy, with no enduring benefit after switching all study subjects to active drug [47].
6. LESSONS LEARNED FROM MAJOR CLINICAL TRIALS

Even if earlier therapy provides a disease-modifying effect, the studies confirming that hypothesis would be expensive and last several years, probably even decades.

In a cross-sectional study using a new PET tracer to visualize aggregated A-beta in dominantly inherited AD [56], A-beta accumulation started at a median age of 28.2 years, which is about 16 years prior to first AD symptoms and 21 years prior to full AD symptoms. Only very well-tolerated and easy-to-use therapies would be eligible for such a long-lasting prophylactic treatment.

As an alternative, better symptomatic therapies, with or without potential additional disease-modifying effects, should again find more attention to provide therapeutic alternatives to the existing cholinergic therapies and memantine. In future, effective disease management will also require multiple approaches.

References

III. CHALLENGES AND OPPORTUNITIES TO CONDUCT GLOBAL AD TRIALS

REFERENCES


6. LESSONS LEARNED FROM MAJOR CLINICAL TRIALS


