Why the Negative Studies in Alzheimer’s Disease?

Hans J. Möbius
EnVivo International B.V., The Netherlands

7.1 INTRODUCTION

This chapter attempts to critically analyze the reasons why there have been so many negative studies and so few successes in developing drugs to treat Alzheimer’s disease (AD) during the last 20 years. During this period a variety of treatment principles were successfully tested in animal models but only two have currently achieved approval as clinical therapies—acetylcholinesterase inhibition and uncompetitive N-methyl d-aspartate (NMDA) antagonism. To date, there have been more than 200 clinical development failures for various reasons and all completed Phase III trials on disease modifying compounds in AD during the past decade have failed to demonstrate a cognitive or clinically relevant improvement.

Of even greater concern are the discrepancies between the positive results seen in animal models, e.g., removal of brain amyloid and failure to show benefit in clinical trials when targeting the same mechanism. Despite major investments and increased understanding of pathophysiology, proof of disease modification remains elusive today. This is in stark contrast to progress in other therapeutic areas where considerable advances have been made, e.g., diabetes or cancer.

This chapter asks fundamental questions about the reasons for the series of negative studies:

- Why has there been so much focus on amyloid in AD?
- Has there been a too simplistic view of the pathophysiology of the disease and the temporal nature of the pathological processes?
• How have issues in the use of preclinical models and their translation compounded the situation?
• Have the methods used in clinical drug development and the refinement of its tools contributed to the lack of success?
• Have researchers failed to consider the impact of demographic characteristics (medical comorbidities, concomitant medications) on course of illness and response to interventions?
• Have researchers failed to learn from previous mistakes in earlier AD drug development programs?
• Has regulatory guidance or lack thereof contributed to the situation?

7.2 WHY HAS THERE BEEN SO MUCH FOCUS ON AMYLOID IN AD?

Historically, the pathophysiology has progressed from initial metabolic considerations (“lecithin depletion”) through regional post-mortem neurotransmitter reduction to the first neurotransmitter-based rational therapy (tacrine) and then the amyloid hypothesis [1], followed by Braak’s paired helical filament (PHF) start and spread law [2]. It has long been generally accepted that the two AD hallmark lesions consist of Aβ plaques and neurofibrillary tangles build up from tau.

However, the publication of the first transgenic mouse model of AD [3] was based on the amyloid hypothesis, and amyloid precursor protein (APP) transgenic mouse models became key to the subsequently intensified search for a rational, causal therapy. Transgenic mouse models of tau were also published but did not lead to a comparable drug screening effort—or less success. In the following years, drug screening and development into late stages was mainly focused on the amyloid cascade hypothesis, with some on inflammation pathways and little on tau alteration. Ten years after the initial publication of the Braak PHF spread and staging approach [2] was correlated to clinical status, Giannakopoulos et al. [4] reported that tangle and neuron numbers, but not amyloid load, predict cognitive status in AD. Yet such reports did not change the mainstay of research and development (R&D). Recent neuropathological data point to tau formation in the olfactory bulb and brainstem even prior to Braak Stage I [5]. It has been shown that Aβ toxicity is tau dependent, although the mechanistic link is unclear [6,7]. Ittner et al. [8] described a less-known dendritic function of tau in post-synaptic targeting of the Src kinase Fyn, which is disrupted by truncated tau, and go on to suggest that tau and tau-dependent mechanisms might thus mediate Aβ toxicity at the post-synapse via NMDA receptor excitotoxicity. To date, not all these mechanisms are fully understood, although this kind of research points to an attempt of a more integrated understanding of the etiopathogenesis as opposed to a predominant focus on amyloid.
The key question of the relationship of “drugable” targets to the course of human disease remains to be better defined. AD is clearly polygenetic and multi-factorial and involves several different etiopathogenic mechanisms—but do researchers and scientists really take this fact sufficiently into account? While it is generally accepted that Aβ oligomers are toxic, it is still not known which “toxic species” of Aβ is/are the appropriate target, how much lowering is required, and in which phase of the illness.

Likewise, it proved very difficult to identify a “drugable” target to stop the formation of toxic tau oligomers and PHF formation; for example, memantine was shown to inhibit hyperphosphorylation of tau [9], but whether that contributes to its clinical effects at all is unclear, and the relevance of tau hyperphosphorylation to PHF formation has been debated [10].

So, 22 years after Hardy and Allsop [1], has the amyloid hypothesis matured into a theory? Increasing evidence points to the fact that amyloid is only part of the picture; how key to the whole picture remains to be elucidated—hence a theory is as yet unavailable. The recent Aβ-directed Phase III failures should not be considered proof of falsification due to the very specific nature of the interventions. Are we any closer to a unifying hypothesis of AD than we were 10 years ago? Probably not. Therefore, the lack of therapeutic progress is in large part due to the lack of a better understanding of the pathophysiological basis and complex nature of AD. This needs to be addressed by basic science not drug development. Only progress on the root causes of AD can lead to a unified theory that in turn can be proven or falsified by further research, both at the preclinical and clinical level.

7.3 HAS THERE BEEN A TOO SIMPLISTIC VIEW OF THE PATHOPHYSIOLOGY OF THE DISEASE AND THE TEMPORAL NATURE OF THE PATHOLOGICAL PROCESSES?

Problems with cognitive impairment, especially executive function, are often signs that patients first notice. These clinical symptoms occur when the pathology has already been present for a decade or longer. Amyloid deposits are accompanied by other changes, for example neurofibrillary tangles, marked synaptic loss, oxidative stress, elevation of cytokines, or mitochondrial dysfunction (Figure 7.1).

AD is a complex disorder that has long been reduced to a one-focus pathology. For the majority of long-term disorders, scientists/researchers/clinicians look at all the processes involved and treat with symptomatic and protective/prophylactic therapies, e.g., diabetes, asthma. In AD research, the focus has been largely on impaired cognition, which likely is the end result of multiple upstream processes involving, for example,
genetic factors, oxidative stress, neuroinflammation, and vascular compromise that in turn result in increased amyloid and tau (see Figure 7.1 [11,12]). It has been hypothesized that one of the main culprits could be cerebrovascular compromise that increases oxidative stress which in turn stimulates neuroinflammation, ultimately leading to a pathway of disease development with plaque and tangle formation in sporadic AD.

Epidemiological evidence suggesting the potential benefit of non-steroidal anti-inflammatory drugs (NSAIDs), oestrogen, statins, and vitamin E in AD has proved disappointing in randomized clinical trials [13] but supports the multi-factorial nature of sporadic AD and the need for diverse interventions and deeper considerations of patient comorbidities and concomitant medications when evaluating response/non-response in clinical trials.

Another source of the perceived failure may be due to direct translation of results from animal models that reflect familial AD whilst the majority of patients in clinical trials have sporadic late-onset AD (LOAD) and one or more physical co-morbidites (see biological factors in Figure 7.1). These other pathogenetic factors that we cannot adequately model are likely to be highly relevant but are often neglected in trial data analyses, or trials are too small or too short to allow for meaningful analyses. Large post-mortem series have repeatedly shown that a significant proportion (>50%) of subjects diagnosed clinically as AD actually had mixed dementia [14]. Likewise, there is still little established insight into the more granular pathogenesis of post-stroke dementia and possible relations to AD. Future preclinical research should aim to combine genetically defined targets with aging (e.g., wt APP in old mice) and include cerebrovascular factors (spontaneously hypertensive rats, diabetic rats, rats with other vascular lesions).

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**FIGURE 7.1** Potential mechanisms of AD pathology. Adapted from [10] and [11].
7.4 How Have Issues in the Use of Preclinical Models and Their Translation Added to This Situation?

There are no animal models of AD that meet all human disease criteria—so there is no actual model of AD. None reflects the structural, connective, functional, and immune system complexities of the human brain; neither can they reflect the time differences that are months in animals versus the decades for human disease to develop. All available animal models aim only to mimic certain aspects of human disease.

There are models of brain aging, brain amyloidosis, tau abnormalities (mutated tau and kinases, tau over-expression), cellular models of tau trans-synaptic and -neuronal transfection, and some combinations of the above. There are no models of altered mitochondrial function, immune response or microglial function, all of which appear to play a tangible role in AD pathophysiology.

So while models have been useful for, for example, understanding a compound’s mode of action, target engagement, and initial dose selection, why is it that out of the treatment principles tested successfully in animal models only the first two in Table 7.1 have resulted in licensed medications?

Animal models of brain aging and AD are often based on defined mechanisms of action, for example the cholinergic deficit in human AD post-mortem tissue or the excitotoxicity theory. These models are based on well-known receptor systems, and pharmacological tools have been

**Table 7.1 Treatment Principles Promoted Based on Animal Models**

<table>
<thead>
<tr>
<th>Successful NDAs/MAAs</th>
<th>Unsuccessful NDAs/MAAs or Never Filed</th>
<th>Still in Development or Never/Not Yet Applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl cholinesterase inhibition (donepezil, galantamine, rivastigmine, tacrine)</td>
<td>Aβ aggregation inhibition (tramiprosate)</td>
<td>Active/passive immunization (FAD)</td>
</tr>
<tr>
<td>Uncompetitive NMDA antagonism (memantine)</td>
<td>Active immunization*</td>
<td>β secretase inhibition</td>
</tr>
<tr>
<td></td>
<td>Passive immunization</td>
<td>γ secretase inhibition and modulation</td>
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<tr>
<td></td>
<td>β secretase inhibition*</td>
<td>Tau aggregation inhibition</td>
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<td>γ secretase inhibition*</td>
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<td></td>
<td>Gingko biloba</td>
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<td></td>
<td>GSK 3β inhibitors</td>
<td>5HT6 antagonism</td>
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<td></td>
<td>Muscarinic, Nicotinic agonists</td>
<td>NSAIDs</td>
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<td></td>
<td>NSAIDs</td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>Vit E, Coenzyme Q</td>
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</tbody>
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*Failed disease modification/slowing of disease progression strategy

FDA: New drug application (NDA); EMA: Marketing authorization application (MAA).
available to validate the mode of action of the research drugs at hand. Memantine has so far been the only drug with a clear effect at the NMDA receptor and a clinical benefit in human disease. Other uncompetitive NMDA antagonists with a similar receptor profile have failed to replicate memantine’s success in the clinic [15,16]. The reasons for this failure remain unclear, as is the relevance of the excitotoxicity hypothesis to human AD. Hence, clear relationships between receptor level lesions and the core symptom cognition were always preferred, for example, in the human scopolamine model of impaired cognition. Obviously, the complex cognitive impairment seen in human AD is only partially mimicked by scopolamine and AD-specific pathology was not important in selecting cholinergic drugs. In this early instance, the phenotypic screening for the core impairment cognition worked, but it has so far failed for all the other approaches.

The “time factor” may further play an important role in the predictability of animal models. Mice allow for a treatment period of about 16 months; this corresponds to 75% of the lifespan of a wild type mouse. In contrast, the human illness duration is 10–20 years, and in addition, clinical trials usually range from 6 to 18 months, which is a fraction of the human lifespan. Clinico-pathological correlation studies have established that there is a continuum between “normal” aging and AD dementia. Build-up of amyloid plaques occurs primarily before the onset of cognitive deficits, whilst neurofibrillary tangles, and neuron and synaptic loss, parallel the progression of cognitive decline [17]. These neuropathological data have been largely confirmed using longitudinal in vivo neuroimaging biomarkers such as amyloid positron emission tomography (PET) and volumetric magnetic resonance imaging [17]. This is a much more complicated picture than that portrayed in the often quoted article by Jack et al. [18]. As summarized in the paper by Kuller and Lopez [19], there are three major hypotheses relating to dementia: amyloid deposition and secondary synaptic loss, vascular injury, and aging.

The importance of, and the potential interaction between these hypotheses is not currently addressed in preclinical research. Other aspects of preclinical research that should be addressed include:

- Gender differences are known in most APP tg mice but their impact on expression of APP and production of Aβ, brain pathology, and behavior remain insufficiently addressed.
- Many transgenic animal models lack precise characterization (e.g., sub-strains with different features).
- The variability of behavioral results is often unknown and power analyses are not used for statistically significant and reproducible “treatment” effects.
- The induction of handling effects on behavioral and learning outcomes is poorly understood and adequate controls not commonly used.
• Too much emphasis is put on study of mode of action and downstream impact on metabolism; too little attention is paid to the investigation of effects on cognition in various models, particularly in the longer term.

• In animal modeling, the same quality principles should be adhered to as in good clinical research, for example data should be scrutinized regarding relevance for human disease, cross-model comparisons, replication in at least one additional model, and relevant safety findings [20]. In a quality survey study of methodology employed in tg mouse models of AD and other neurological conditions, Egan et al. [21] reported randomization in 15%, a blinded outcome assessment in 21%, and a prospective sample size and power calculation in 0%.

• There is a propensity to ignore (and not report) negative data and to embrace positive data without careful replication.

Other factors that potentially contribute to the failure of translation from preclinical to clinical research are:

• Lack of knowledge about the exact toxic species of Aβ and therefore lack of a common functional outcome measure in animal research.

• Blood–brain-barrier pharmacokinetics and pharmacodynamics (in both animals and/or humans) do not support availability of the molecule for treatment of central nervous system (CNS) disorders (e.g., tarenflurbil, pGP substrates).

• Insufficient target engagement at the achieved brain concentrations.

• The pharmacodynamics of the molecule are such that animal tests may show short-term effects but long-term benefits will be lacking and/or detrimental effects will be produced (e.g. segamacestat vs. gamma secretase modulators (GSMs)).

For example, tarenflurbil achieves only low brain levels after nine days of treatment in young Tg2576 mice [22]. Furthermore, short-term treatment with tarenflurbil did not reduce brain Aβ 1–42 and 1–40 levels [23]. Therefore, the preclinical data for tarenflurbil hardly justified the move into clinical trials, at least from an amyloid hypothesis perspective.

In the case of γ secretase inhibitors, whilst acute dosing with both segamacestat and BMS-708163 improved memory deficits in APP tg and non-tg mice, the effects disappeared after eight days of sub-chronic dosing. The authors [24] suspect that synaptic accumulation of beta-C-terminal fragments in the hippocampus caused this loss of benefit. They go on to show that second generation GSMs ameliorate memory deficits in tg mice and wild type, both acutely and sub-chronically. Should the different functional consequences of gamma secretase inhibition (GSI) versus modulation (GSM) have been predicted?

Although animal models certainly cannot reliably predict (serious) adverse effects, researchers need to be alert to preliminary evidence
of potential side effects in their work. The brain-specific adverse event vasogenic edema, now summarized under the term “Amyloid Related Imaging Abnormalities with Parenchymal Edema (ARIA-E),” was predicted from the tg mouse model [25]. This is thought to be due to the accumulation of monoclonal antibody antigen complexes in the brain vasculature. However, such effects when they do occur require serious investigations and consideration. Should the increased risk of skin cancer with segamacestat have been anticipated because of potential “off target” effects at Notch [26]?

7.5 HAVE THE METHODS USED IN CLINICAL DRUG DEVELOPMENT AND THE REFINEMENT OF ITS TOOLS CONTRIBUTED TO THE LACK OF SUCCESS?

Why do we still employ trial designs from the early nineties (placebo-controlled, double-blind, parallel group) instead of advancing the field by innovative trial designs that were proposed over a decade ago [27]? Instead, discussion has focused on “secular change” supposedly causing loss of placebo decline, which was shown not to be the case [28]. Pharmaceutical companies have also shown a “herd mentality,” i.e., a reluctance to change their approach despite the increasing number of failed trials.

A recent review by Cummings et al. [29] outlines alternative trial designs and their merits. For example, Bayesian adaptive clinical trials could be particularly useful in Phase II as they allow the use of data collected in the trial to modify doses, sample size, trial duration, and entry criteria in an ongoing way. Futility designs permit the use of historical controls and may shorten the duration of trials of potential disease-modifying or -slowing agents. In complex disorders combination therapy is the rule rather than the exception; trial designs need to allow for investigation of potential additive or synergistic treatment effects.

Despite the availability of a wide range of scales to assess cognition, functional ability quality of life, behavioral and psychological symptoms, caregiver costs and reducing costs of illness, many of these measures have significant shortcomings [30]. Aspects of cognition that are infrequently addressed by current scales include misidentification, learning aptitude, decision making, self-determination, and disturbed/slowed response to external stimuli. Equally, issues with communication and social interaction such as responsiveness, correct use and interpretation of gestures, implementation of commands, cooperation in care and daily living, social involvement, adaptability, relationships with family and friends, and intimacy of contacts (informal/formal) are also rarely addressed. The majority of instruments have significant limitations
with respect to sensitivity to stages of disease and changes over time. Ideally one would like to have a new instrument that can assess multiple domains at all stages of AD whilst remaining sensitive to changes and therapy effects. Scales such as the Clinical Dementia Rating Sum of Boxes (CDR-SB) that combine cognitive and functional assessments and have sensitivity across stages of disease are a step in this direction [31]. However, there is still a need for a new multi-domain and easy-to-administer AD scale for the assessment of disease progression and response to therapy.

With the increasing trend for multinational clinical trials has come the need for more attention to consistency across sites for all aspects of the trial. This includes patient recruitment and assessment, interpretation of outcomes that have been translated into different languages, standardization of assessment techniques (psychometric scales as well as electrocardiograms, laboratory tests, neuroimaging), and interpretation of tests. Many companies now specialize in rater training and translation of scales but no one body ensures that training, application, and data analysis are consistent with one another.

The availability of new tools also influences the research focus. With the recent approval of the amyloid imaging agent, florbetapir, for research purposes, there has been renewed emphasis on the amyloid hypothesis. If we are to make progress, researchers need to be mindful of the complexity of AD and the need for equivalent investment and development of assessment tools and biomarkers for other aspects of the disease.

In this era of personalized medicine there is a move towards individualized therapies. This approach is inconsistent with the current considerations in Phase III clinical trials where generalization to as wider population as possible is the aim. Most clinical programs aim to study one potential aspect of the pathophysiology, but it is clear that AD as defined and captured by our current diagnostic systems is not a uniform disease and rather consists of mixed neuropathologies.

7.6 HAVE RESEARCHERS FAILED TO CONSIDER THE IMPACT OF IMPORTANT DEMOGRAPHIC CHARACTERISTICS ON THE COURSE OF ILLNESS AND RESPONSE TO INTERVENTIONS?

There is a growing body of data from clinical trials, epidemiological studies, and studies in clinical practice that demonstrate that a range of patient factors (comorbid conditions, concomitant medications) can impact on cognitive decline and its rate of progression. Evidence from pharmaceutical research suggests that most of these factors are not

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considered in recruitment to clinical trials, prospective stratification, or in analyses of the efficacy and risk–benefit.

Physiological impairment of renal function is a function of age and is common in the elderly. There is a growing body of evidence showing that even mild renal impairment is associated with increased risk of cardiovascular and cerebrovascular events with a more rapid rate of cognitive decline in the elderly [32], a factor that is rarely accounted for in clinical trial analyses.

Using a modification of the Cardiovascular Health Study Criteria to define frailty that includes weight loss, exhaustion, weakness, slowness, and low physical activity, the Italian Study of Aging showed that frailty is a short-term predictor of overall dementia and vascular dementia [33]. Another aspect to consider is the growing body of data linking vascular risk factors (diabetes, hypertension, raised cholesterol, smoking) with increased susceptibility for AD and other factors (angina, atrial fibrillation, hypertension) with increased rate of decline [34]. Clinico-pathological data also show that people with both vascular disease and AD pathology show either more severe cognitive impairment during life than those with pure AD. The relationship between vascular risk factors is not fully understood. It is thought that vascular and neurodegenerative mechanisms develop in parallel and that vascular disease acts synergistically with AD pathology. The degree to which vascular factors contribute to dementia will vary from individual to individual, giving the likely scenario of a continuum from relatively pure AD through mixed dementia to vascular dementia. The inter-relationship between vascular factors, dementia sub-type, and progress of cognitive decline has important implications for clinical trials, especially for patient recruitment and assessment of efficacy. To date most trial sponsors have not paid much attention to these aspects that are likely to have contributed to the reasons for failure.

When looking at the standard primary outcome variable in AD clinical trials, the Alzheimer’s Disease Assessment Scale-cognitive portion (ADAS-Cog), it is interesting to note the factors that can influence rate of change or progression [35]. Covariate analyses indicate that baseline Mini-Mental State Examination (MMSE) score, education, age, and apolipoprotein3/4 genotype had a significant effect on the level and shape of the trajectories of the mean model predicted ADAS-Cog change from baseline. It has been appreciated previously that cognitive decline is not linear. What has been less appreciated is that analysis in different patient sub-populations is warranted to confirm and generalize the findings of the present analysis to consider the indirect response model as a reference model for characterizing the time course of AD.

It is now generally recognized that there is considerable overlap between the risk factors for AD and vascular dementia (VaD). Indeed AD, VaD, and mixed dementias are generally regarded as discreet diagnostic
entities. However, the risk factors such as cardiovascular and cerebrovascular disease, and metabolic disorders (diabetes, obesity), are features of all these dementias. It would seem more relevant to focus on determining the mechanisms by which vascular and neurodegenerative mechanisms jointly contribute to the development and progression of aging-related cognitive disorders rather than considering them as separate diseases. In these respects the degree of control of physical co-morbidities (hypertension, diabetes mellitus) and the impact of long-term treatments by medications to treat these disorders needs more detailed consideration in the selection of study participants and in the sub-group analyses of response to interventions.

7.7 HAVE RESEARCHERS FAILED TO LEARN FROM PREVIOUS MISTAKES IN EARLIER AD DRUG DEVELOPMENT PROGRAMS?

An important aspect of learning from previous experience is to consider both the positive and the negative aspects. However, in research there is the longstanding issue of failure to disclose negative trial results. In preclinical research, Li et al. [36] report on a data mining effort covering the years 2001 to 2011 in which they identified more than 146 substances and treatment modalities tested in 11 transgenic mouse models including APP, tau, double- and triple-cross transgenic mice. Far from all of the results have been published. Irrespective of that fact, while research compounds test positive in such models, there is a widespread perception that animal models appear to have little if any predictive value, because drugs continue to fail in clinical trials.

The history of the vaccination therapy approach in AD is a clear example of where detailed evaluation of the reasons for failure of translation is warranted. Total Aβ deposition as shown by immunohistochemistry was markedly reduced in tg mice after eight weeks of systemic anti-Aβ antibody administration [37]. The same principle was evidenced in humans not only by the initial active vaccination trial with AN1792 in post-mortem data from patients that died due to encephalitis [38], but later also using 11C-PIB PET in vivo after 78 weeks of bapineuzumab treatment. So the mechanistic basis for the elimination of Aβ deposits appeared confirmed. Moreover, Morgan et al. [39] showed that tg mice benefited significantly from Aβ1–42 immunization at the age of 7.5 months when tested later in the radial water maze at the age of 15.5 months, suggesting that also the functional proof of concept was established before the start of late-phase clinical trials.

As known today, cognitive improvement was neither shown in the follow-up of AN1792 survivors nor in the bapineuzumab Phase III trials.
In the two solanezumab Phase III trials (Expedition 1 and 2) for mild to moderate AD patients, benefit on the primary endpoints (cognition and function) did not differ significantly from placebo. However, in a pre-specified secondary analysis, slowing of cognitive decline was shown in patients with mild AD and a number of biomarkers showed an effect of solanezumab. The results of trials with monoclonal antibodies deserve more detailed scrutiny to determine the potential implications for further evaluation in early AD.

There is also evidence of a continued reluctance to look critically at data from early-phase clinical trials, with the result that programs are progressed to later-phase development with inadequate evidence of efficacy and/or safety, and then fail. Such late-stage failures make a major contribution to the high cost of drug development [40]. In 2011, these concerns prompted the Alzheimer’s Association to convene a Roundtable discussion involving scientists from academia, industry, and government regulatory agencies to review the lessons learnt and discuss strategies for improving Go–No go decision making about the probability of Phase II trial results predicting success in Phase III [41].

In summary, the following lessons are learnt:

- Phase II trials should explore the dose/exposure–response relationships and show proof of mechanism (i.e., that the target has been engaged in the CNS).
- The target must be active and relevant with respect to therapeutic manipulation in the phase of the disease being studied.
- Biomarker selection and outcomes should be consistent with expected actions of drugs, or pathways related to the target.
- Pharmacokinetics and pharmacodynamic modeling should be used to optimize dose and dosing regimen selection.
- Phase II trials would demonstrate that clinical endpoints are affected, although the difficulties in assessing clinical effects in small Phase II trials with short durations are acknowledged.
- In planning for studies of earlier-stage disease, the goal remains to demonstrate efficacy that is clinically beneficial.
- Data from failed proof-of-concept trials should be rapidly fed back to the drug discovery process to improve the understanding of mechanisms.
- Data from all clinical sub-groups, post hoc, or other types of secondary analyses are important, but they are also potentially misleading when not subsequently tested prospectively.

The focus has been on development programs that target the largest possible market with the broadest labeling when smaller, more focused target labels were likely to be more successful; for example, there was more success in Parkinson’s disease dementia and Lewy body dementia with
cholinesterase inhibitors. A recent article by Boxer et al. [42] suggested that Frontotemporal dementia (FTD) should be considered an attractive target for developing therapies for the following reasons:

- The clinical and molecular features of FTD, including rapid disease progression and relatively pure molecular pathology.
- Consensus diagnostic criteria will facilitate the identification of patients.
- A variety of neuropsychological, functional, and behavioral scales have been shown to be sensitive to disease progression.
- Quantitative neuroimaging measurements demonstrate progressive brain atrophy in FTD at rates that may surpass AD.
- The similarities between FTD and other neurodegenerative diseases suggest that FTD researchers will be able to draw on this experience to create a road map for FTD drug development.

7.8 HAS REGULATORY GUIDANCE OR LACK THEREOF CONTRIBUTED TO THE SITUATION?

While the Food and Drug Administration (FDA) issued a first AD Guidance in 1990 [43], its status has not been elevated from “draft” since then. The first European Medicines Agency guidelines on dementia were issued in 2005 and revised in 2008 [44] to include, for the first time, important advice for clinical researchers on how to translate drugs with a disease-modifying potential into feasible trial designs—of note, introducing of a two-staged approach where “delay of disability” could represent an earlier, and “disease modification” a later, labeling target. In 2013, and in keeping with the broader understanding of AD as a continuum spanning decades until initial clinical symptoms become apparent, the FDA issued a new draft guideline for early or prodromal AD [45], overcoming some of the trial design limitations of the past. Given the proportion of required investments into late-stage clinical development in AD, these later regulatory guidances are very welcome as, due to the many prior failures, “Big Pharma” as well as venture capital is asking for more “investment security.” For all the reasons listed above, it appears highly debatable whether regulatory history has had any tangible influence on progressing the current situation.

7.9 SUMMARY AND CONCLUSIONS

In light of the demographic “AD tsunami” ahead of all developed societies, the medical need for effective symptomatic and disease-modifying drugs could not be higher. After two decades of chief focus on the
amyloid hypothesis, and the large failures of amyloid-based Phase III programs, there is clearly a momentum for broadening the horizon to refine the amyloid approach and to include a wider range of modes of action, alone and in combination, particularly tau, neuroinflammation, oxidative, and metabolic stress.

There is an increased interest in tau immunotherapy as it was shown to reduce tau pathology, facilitate p-tau clearance, improve cognition in animal models, and potentially delay progression [46], and might serve an integrated approach at combined Aβ and tau toxicity mediated via NMDA receptor excitotoxicity [47].

Scientists are taking a wider view of dementia and demonstrating a greater appreciation of the impact of the similarities and differences both within and between dementias. Different factors influence the age of onset and rate of progress of familial and sporadic AD. The increased appreciation of AD as a syndromal diagnosis rather than a single distinct entity will support the identification of targeted therapies, e.g., against familial AD.

Meanwhile, available opportunities for designing prevention trials that target modification of risk factors for dementia, such as aggressively treating raised blood pressure and poorly controlled diabetes, should receive greater consideration. Such trials are not without their own set of challenges, i.e., which patients, which intervention(s), what duration of follow-up, etc. Even then life is not simple, as illustrated by the effect of age on the risk of dementia associated with raised blood pressure; this risk decreases with increasing age. Therefore, if one was designing a trial looking at the impact of improved blood pressure control on dementia risk, one would want to enroll younger patients (say, 65 to 75 years) rather than older patients.

Over and above patient heterogeneity, another factors that has undermined the potential success of clinical trials for AD is the lack of standardized methodologies. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is an excellent example of how collaboration among researchers and scientists in academia and the pharmaceutical industry can result in major advances in the understanding of AD [48]. The group has not only developed standardized methodologies for assessments (clinical tests, cerebrospinal fluid analysis, neuroimaging) but has also improved diagnostic categorization, advanced the understanding of biomarkers and genetics, and determined how the rate of change of outcomes differs between controls and patients with AD. Importantly, the group also developed a platform for data and information sharing that will hopefully stimulate more research and help clarify competing hypotheses and answer as yet unresolved questions about AD.

Biomarker development and validation will be ever-more important in a number of potential ways, for example to define susceptible...
populations, to confirm interaction with the selected target, to determine response/non-response, and to determine liability to safety issues. In their paper about the development of biomarkers to chart all AD stages, Hampel et al. [49] describe the need for biomarkers that could address the sources of “systems failure” during the entire course of AD as a prerequisite to:

- Improving and accelerating drug development;
- Facilitating the identification of biochemical effects of a drug in short-term pilot studies;
- Selecting, enriching, and stratifying specific patient and target populations;
- Assessing the effects of treatment on disease progression and outcome.

Such markers should enable better selection of drug candidates, better verification of the mechanism of action, clearer definition of dose effects, shortening of trial durations, reduction in sample sizes and costs, and improvement in recruitment and retention of study participants.

None of the known AD susceptibility variants were shown to be significantly associated with the rate of cognitive decline except for ApoE and CR1; last but not least, gene expression studies in conjunction with neuropathology and cognitive endophenotypes might become a more useful approach than genome-wide analyses to discover novel AD susceptibility genes and pathways [12].

Looking to the future, we cannot afford to falter. Through a broader, more integrated vision of dementia [50], remembering the appropriate use of animal models, consideration of wider demographic variables (co-morbid illnesses and genetic influences), critical evaluation of preclinical and clinical methodology and data, as well as learning from other therapeutic areas, and a greater collaborative effort (e.g., ADNI and the Coalition against Major Diseases), there is hope for greater success.

References

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7. WHY THE NEGATIVE STUDIES IN ALZHEIMER’S DISEASE?


REFERENCES


7. WHY THE NEGATIVE STUDIES IN ALZHEIMER’S DISEASE?

