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Clinical translation potential from animal to human in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a chronic, progressive, and neurodegenerative disorder. Five drugs approved by FDA to treat Alzheimer's disease. The first four are Donepezil, Memantine, Rivastigmine, and Galantamine. The fifth one is a fixed dose combination of Memantine as well as Donepezil. All these drugs treat Alzheimer's only symptomatically. So, there is an urgent need to investigate a drug that can provide both symptomatic as well as curative treatment for Alzheimer's. Huge experimental research is going on but still, there is a lack of translation potential of experimental data into clinics. Various factors are responsible for this which include lack of efficacy, severe adverse effects, complex genetics, difficulty in the recruitment process of AD clinical trials, lack of understanding of the disease pathology, or complex pathophysiology of the disease. There are various ways to address these challenges in dementia research which include increasing the funding for dementia research, increase in public awareness of AD and other dementia, incorporating dementia research into the care continuum, improving access to clinical trials, and decreasing risks of the drug development process of AD. Therefore, in this review, preclinical limitations which hamper the drug development process for the treatment of Alzheimer's disease are summarized.

Keywords: Alzheimer's disease, Amyloid beta, Acetylcholinesterase inhibitors, preclinical studies, clinical trials, pathophysiology

1. Introduction

Numerous CNS illnesses have been linked to oxidative stress, and neuroscientists have unearthed much data supporting this hypothesis. Neuronal biochemical cascades may be jeopardized, neuroplasticity may be impaired, and aging may be hastened by excess reactive oxygen species (ROS) [1]. It is worth noting that full functional status necessitates satisfying a high energy demand in the CNS, which in turn causes an excess

formation of reactive oxygen species (ROS). The central nervous system's antioxidant agents rigorously maintain the overall balance of reactive oxygen species (ROS), although age-related neuronal alterations may reduce their effectiveness [1, 2].

AD is a progressive neurodegenerative disorder that persistently causes cognitive decline, memory loss, various behavioral changes, and alteration in brain functionality [2]. The most common symptom associated with AD is dementia. AD is named after the name of scientist Alois Alzheimer in 1907. It mainly affects people of the age group 65 years and older. Aβ is the main protein responsible for causing the disease [3]. It has been shown that complete clinical signs and symptoms of AD take around 10-15 years the development. There is another protein named tau whose hyperphosphorylation causes further neuronal degeneration. Alzheimer's has been classified into various stages which progressively get intense as proceeds [4]. So there is an urgent need for a drug that can effectively eradicate the disease with a complete cure. As already five drugs have been approved by the FDA which include Donepezil (Aricept), Galantamine (Razadyne), Rivastigmine (Exelon), Memantine, and a fixed-dose combination of Memantine and donepezil. But still, there is a very big disadvantage of these medications that they all provide only symptomatic treatment but not curative treatment. Statistical analysis has shown that by 2050, every 1 person will be affected with disease out of the 85 persons [5]. The most common symptom of AD is dementia which happens in case of the 60-80% of people. Various co-morbid conditions are also associated with Alzheimer's which includes genitourinary disorder, diabetes, cardiovascular disease, and musculoskeletal pain. Some other neurological co-morbid conditions include anxiety, depression, and apathy [6]. Many drugs under the developmental process for the treatment of AD which were proposed to clear the Aβ plaques from the brain have shown to be failed in phase III of the clinical trial. Many clinical trials have failed to develop a drug that can specifically treat this particular disease. There are a lot of problems that have been found that cause the failure of these clinical trials. Here are the key reasons:

Reasons:**1.** The recruiting patients don't have that much specificity

Reason **2.** Qualification is not sufficient for the patients which are recruited for the clinical trial

Reason **3.** Drugs that are developed for Alzheimer's target the wrong substrate that results in an unsatisfactory result

Reason 4. It may be the drug therapy started too late to show its effects and application of the wrong methodologies [7]. As it's a progressive disease its symptoms take many years development and when the first symptom start appearing then already AD has shown irreversible damage to the brain [8]. So this can also be one reason for the late diagnosis as well as the start of the therapy. Another big hurdle for the development of drugs for Alzheimer's is that there is a lack of surrogate biomarkers for the disease progression. It is observed that the failure rate is too high which almost 99.6% since 2002 is. It reflects the inefficiency of the clinical trials. This needs urgent steps for improvement. Several factors are associated with the development and degeneration of Alzheimer's. Proper diet and lifestyle are important. Cholesterol is found to be associated with the ApoE mutation is a major gene responsible for the oligomerization of Aβ that further leads to the Aβ plaque formation [9]. It has also been found that there is another compound that is omega-3-fatty acid which has been shown to

reduce Alzheimer's disease progression along with that it has shown some neuroprotective as well as anti-inflammatory effects [10]. Other than this many other variables are responsible for Alzheimer's pathology that includes diet, education, occupational fulfillment, leisure participation, multilingualism, trauma, sleep, cognitive testing, coaching, stressors in clinics, concomitant illnesses, medication interactions, and the fundamental heterogeneity of AD [11]. Some other reasons include a lack of disease pathology understanding, the mechanism of action of various drugs remains unknown, and the study design is not adequate to fulfill the requirement [11]. Various reasons have been given for the failure of clinical trials. Antiacetylcholinesterase drug therapy which increases acetylcholine levels in the brain used to treat Alzheimer's has also been shown to be failed in AD preclinical trials. Various factors have been shown that leads to the failure of AD clinical trial designs which include food supplement, mental workload, physical workload, and insufficient sleep which are the major factors that disturb everyday life. Clinical factors are another category that leads to such problems including undesirable drug interactions, and co-morbid conditions [11]. Other than these factors some errors create problems in AD trials translation potential which includes an instrumental error, methodological error, and measurement error which comes under the category of intrinsic factors other extrinsic factors include patient factor, wrong study design, and wrong drug administration [12]. Therefore, overall in this article, we are critically going to analyze why there is a huge hurdle in translating preclinical research data into clinical research data in AD and these challenges can be tackled.

2. An overview of epidemiology, pathogenesis, clinical manifestations, and current treatment strategies for Alzheimer's Disease

The number of persons with dementia is believed to be over 50 million worldwide. This number is predicted to double every 20 years, reaching 131.5 million by 2050 and 75 million by 2030 [13]. Dementia-related illnesses, in particular, are projected to become more common in the future decades than cardiovascular disease and cancer combined [14]. Dementia has different categories and Alzheimer's is one of the most obvious reasons for dementia. Age is the primary risk factor for Alzheimer's disease.

More research in the matters of cellular signaling networks and molecular changes including aetiology is necessary to understand the development and prognosis of the disease [15].

Research into the interaction between cellular and molecular signaling networks and the aetiology of Alzheimer's disease is still necessary for progress toward this aim [15].

The "Amyloid Hypothesis" of Alzhemer's mentions that a major flaw in the production and accumulation of beta-amyloid is the primary cause of the disease [16].

Many other sized peptides are produced when APP is broken down, but A40 and A42 are the most well-known because of the pathological amyloid cascade they initiate. When the amount of A42 to A40 increases, neurotoxicity is triggered by the accumulation of A fibrils. In AD, it is found that genetic, metabolic, or

environmental stressors become more active when they are backed by NFTs and A. This causes several neural cell deaths leading to AD [17]. Dementia starts showing diverse symptoms when A's disposition increases that stimulating microglia and astrocytes. This then triggers pro-inflammatory flows that can damage axons and dendrons. The obvious consequence is disrupted synaptic interactions leading to cognitive dysfunction [16]. Evidence suggests that synaptic damage related to memory impairment occurs in the initial phases of AD [18].

The clinical stages of the disease are closely connected to over excitability of glutamatergic receptors and the degeneration of "cholinergic neurons" in the brain's cortex and hippocampus parts.

Alzheimer's disease (AD) has three clinical stages:

a. The pre-clinical stage

This stage involves mild cognitive dysfunction including loss of memory. Some minute neuropathological changes take place at this primary stage of AD that involves changes in cortical regions [18].

b. The mild early stage:

This stage is characterized by some obvious symptoms such as mood disorders, difficulty in focusing on some jobs, difficulty in calculating, and memory derangement [19].

c. The moderate stage of Alzheimer's disease

Characterized by the gradual spread of the disease to neighboring cortical regions The last stage severely impairs not only cognitive and memory abilities but also familial and behavioral harmony [20].

For AD treatment two types of drugs are currently approved. The first one belongs to the category of Acetylcholinesterase (AchE) inhibitors [21]. The second one belongs to the category of N-Methyl – D – Asperate receptor antagonists [22]. These two categories of drugs control the neurotransmitters within the brain enhancing the level of Ach. The drugs do so by controlling the degradation of Ach. Galantamine and memantine can also be applied to alleviate the symptoms but these drugs couldn't cure AD.

The pathophysiology of AD is a bit complicated. The main pathological features of the disease include amyloid plaque deposition and hyperphosphorylation of tau protein. Various brain areas which are mainly affected causing Alzheimer's include the hippocampus, amygdala, and entorhinal cortex [23]. Several hypotheses have been put forward which are responsible for Alzheimer's involving the cholinergic hypothesis, Aβ hypothesis, oxidative stress, and tau hypothesis [24]. Other than these hypotheses, various genetic factors are also responsible for the pathogenesis of Alzheimer's disease e.g. mutation in Presenilin 1, Preseniline 2, and amyloid beta precursor protein [25]. In the case of Alzheimer's disease, there occurs loss of neurons mainly in the CA1 region of the hippocampus whereas neuronal tangle formation correlates with the severity of dementia. In the case of the amyloid hypothesis, APP is cleaved by alpha, beta, and gamma-secretase producing Aβ

peptide which causes an imbalance between amyloid beta production and clearance. This Aβ spontaneously leads to plaque formation resulting in the disruption of neurons, and toxic oligomer formation [26]. Another main factor that is responsible for Alzheimer's pathophysiology is the tau protein. In normal circumstances, tau is present in the unphosphorylated form. This is the main microtubule-associated binding protein. In previous studies, it has been shown that tau protein gets hyperphosphorylated by various protein kinases. As tau protein is responsible for the microtubule assembly which gets distorted by hyperphosphorylation of the tau protein [27]. There is another main parameter that is involved in the pathogenesis of Alzheimer's. This is called oxidative stress. Amyloid beta is responsible for the overproduction of Reactive oxygen species that mainly causes lipid peroxidation, it also affects the regulation of calcium homeostasis which decreases ATP production, and DNA damage [28].

Table 1. The role of endogenous antioxidant compounds in Alzheimer's disease progression.

Natural product	Antioxidant role in AD	Reference
Melatonin	Reduces amyloid fibril production, controls free radical removal, and prevents oxidation of biomolecules.	[29]; Matsubara et al., 2003
N-salicyloyl tryptamine derivatives, melatonin	Anti-inflammatory characteristics (decreases the production of ROS, COX-2, PGE-2, iNOS). Lowers GFAP and Iba1in the hippocampus region.	[30]
Coenzyme Q10	Reduces intracellular beta-amyloid peptide accumulation and apoptosis by an adequate amount.	[31, 32]
Vitamin E	Enhances neuroprotection.	Kryscio et al., 2017
Twendee X®	Reducing reactive oxygen species (ROS) has been linked to enhanced cognitive function, decreased A sedimentation, and increased tau phosphorylation.	[33], Liu et al., 2019,
DHA	Amyloid formation decreases.	Lopes et al., 2011; [34, 35]
Curcumin, quercetin, and tannic acid	Guards against amyloid plaques and NFT buildup.	[36]
Polyphenols	Anti-amyloidogenic, anti-inflammatory, and anti-apoptotic properties; reversible role in cognitive deterioration; neuroprotective properties.	[37]
Flavonoids	Down-regulate reactive oxygen species (ROS) production, down-regulate inflammatory genes, down-regulate amyloid sedimentation, and regulate cellular development and differentiation.	[38]
Resveratrol	This shows effective antioxidant characteristics. Moreover, helps to reduce amyloid sedimentation to a great extent.	[39]

Phenolic acid	Increases the level of antioxidants that help to drain out free radicals. Moreover, inhibits COX-2, Caspase – 3, and MAPKp38.	[40]
Rosmarinic acid	Decrease Aβ growth, recover synaptic parameters, recover neurogenesis, and inhibit Aβ oligomerization.	[41]
Huperzine-A (HupA)	This one is an AchE inhibitor. It can overcome the blood-brain barrier. It can control ROS production and oxidative stress. Protects the brain from glutamate toxicity. Boosts antioxidant activities. Regulate proteins like P53, Bcl – 1, and Caspase- 3.	[42]; Wang and Tang 2005; [43, 44]
Ginkgo biloba	Memory enhancement. Reduce anti-inflammatory and phospholipid peroxidation. Minimize the ratio of β-amyloid accumulation.	Liu, et al., 2020; [45]; Ihl et al., 2012; [46]
Curcumin	Inhibits ROS development reduces chronic inflammation and inhibits Aβ accumulation.	[47]b
Bacopa monnieri	Neuroprotection, Inhibitor of AChE.	Bhattacharya et al., 2000; Das et al., 2002
Brahmi - Bacopa monnieri	Blocks Aβ production, inhibits neurodegeneration, and enhances memory performance.	[48]
Ashwagandha, Withania somnifera	Reduces Aβ production and neural apoptosis. Re-establishes synaptic function. Controls mitochondrial dysfunction. Improves cognition.	[49]
Uncaria tomentosa	Inhibits plaques and tangles formation.	[50]
Centella Asiatica	Decreases amyloid beta levels and enhances cognition.	[51]
Centella Asiatica	Revert the Aβ-induced neuropathological.	[52]
Glycyrrhiza glabra	Improves memory.	[53]
Lepidium meyenii	Memory potentiation.	[54]

Tinospora cordifolia	Neuroprotection.	[55]
Convolvulus pluricaulis	Improvement in basic cognitive abilities.	[56]

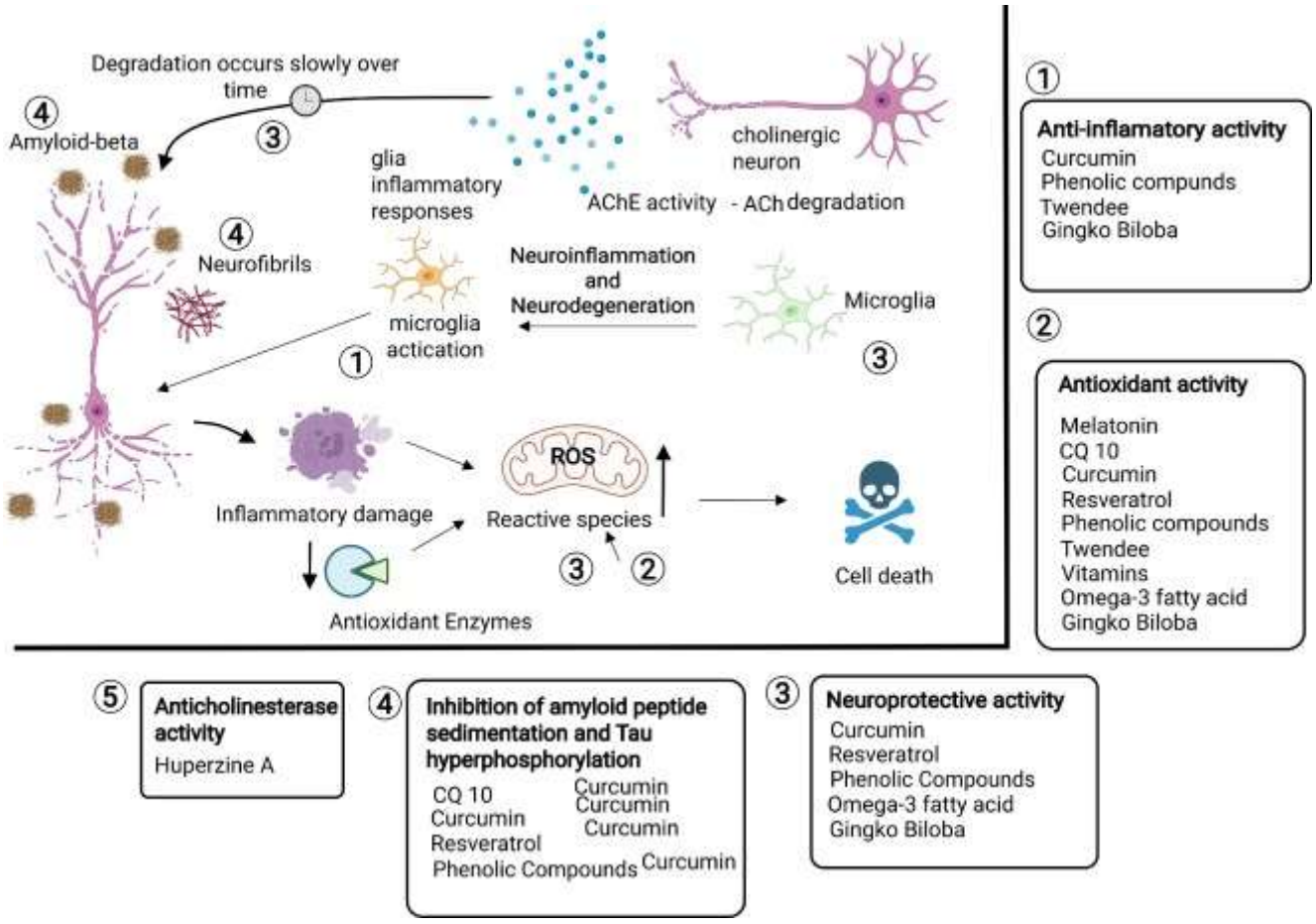

Fig. 1. *Overview of the intertwining between natural antioxidant molecules and AD pathology. The figure summarizes the mechanism by which various natural antioxidant compounds protect against AD pathology (represented by numbers). Number 1: represents examples of antioxidants that inhibit neuroinflammation; number 2: inhibition of ROS mitochondrial formation; number 3: neuroprotection mechanism through deceleration of neurodegeneration, controlling of brain metabolism, dampening of oxidative stress and inflammation; number 4: inhibition of amyloid sedimentation and tau fibrils formation; number 5: inhibition of acetylcholinesterase activity (ACh - Acetylcholine, AChE - acetylcholinesterase). BioRedear created the figure.*

3. Various Hypothesis involved in AD

Table 1. Drugs under clinical trials for AD

Sr. No.	Reference	Drugs	Mechanism	Patient No.	Types of clinical trial	Design	Remarks	Conclusion
1.	Jing-Ying *et. al*.	ZT-1 (Prodrug)	Selective Antiacetylcholinesterase	9	Three-way latin square design	Double-blinded, Placebo Controlled	Pro-drug, Rapidly absorbed	Well tolerated in all Male healthy volunteer
2.	Maelicke A *et. al.*	Memogain	Antiacetylcholinesterase, Antibutrylcholinesterase MAO-A and MAO-B inhibitory activity	-	-	-	Free from gastrointestinal side effects	Used for mild to Moderately severe Alzheimer's dementia
3.	Alzaforum	NGX267 (AF267B)	Acetylcholinesterase inhibitor, a direct activator of the cholinergic system	-	-	-	-	Improved spatial memory in 3xTg-AD mice
4.	Clinicaltrial.gov	Aducanumab	Anti-amyloid (Monoclonal antibody)	1605 (Prodromal)	Interventional	Randomized Double-Blind, Placebo-Controlled	Slow neurodegeneration and disease progression	Trial was halted in March 2019
5.	Clinicaltrial.gov	Albumin + Immunoglobulin	Anti-amyloid (Polyclonal antibody)	350	Interventional Study	Multicenter Randomized Controlled	Effect on cognition, behavior, and functioning assessed with standard neuropsychiatric tests.	Trial is active
6.	Clinical trial.gov	ABT-957	Acetylcholinesterase inhibitor	19	-	Randomized	-	The trial has been terminated

7.	Clinical trial.gov	CT-1812	Displace amyloid beta from CSF	18	Parallel	Randomized double-blind, placebo-controlled	-	Drug is withdrawn

4. Various drugs under different phases of a clinical trial for Alzheimer's Disease

- **ZT-1 (Prodrug):** The newly discovered natural product is ZT-1 which is a prodrug (it is inactive as such but gets activated by the enzymatic activity inside the gut). It can act as an anti-acetylcholinesterase (AChE). It has a cognition-improving effect. It is the drug that is under clinical trial specifically in Phase-II_b.
- **Memogain (Prodrug):** There is another prodrug that is Memogain which is inactive as such. It has very high bioavailability. It has a cognition-enhancing effect. It is a highly potent drug. There is another compound Bis-(aralkyl) amino and (hetero)aryl which have a neuroprotective effect. There is another highly potent drug compound that is ladostigil which have both neuroprotective as well as Ach-butyrylcholinesterase and MAO-A as well as MAO-B activities are also inhibited. It has been shown that the phase II clinical study has been done on this compound and is under developmental process.
- **NGX267(AF267B):** Another compound named NGX267 (AF267B) has an agonistic activity for the muscarinic receptor (M1) and a cognition-enhancing effect. It has shown its effect on the reduction of tau protein as well as Aβ ($Aβ_{1-42}$) and tau pathologies [57]**.**

Summary

Many studies are going on to carry out various clinical trials which had shown that overall clinical trials possess about 63% of the agent,23% of the agents have a cognition-enhancing effect, and another drug used to control the various neuropsychiatric symptoms.

The agents have been counted in various phases of the clinical trials [58]:

Phase I: This clinical trial involves 8 new agents.

Phase II: This clinical trial involves 14 new drug agents.

Phase III: This clinical trial involves 8 new chemical compounds.

5. Complexity of the disease

Alzheimer's has a very complex form in nature. Several path physiological parameters are associated with the disease which includes an accumulation of the Aβ protein. Aβ production takes place by APP and it

has been supposed to metabolize by protease and various other lysosomal enzymes. Aβ is the main protein which got accumulated in the brain of a diseased patient and acts as the main pathological hallmark of the condition. So it mainly acts as the main potential target for drugs. Aβ deposition leads to a huge amount of neuronal degeneration. Aβ in excess leads to the stress of the mitochondria which releases the ROS (Reactive oxygen species) and further causes neuronal cell death. Aβ has also been found to induce cell apoptosis by interaction with the various cell surface receptors. Various processes take place for the removal of the overproduced Amyloid-β which mainly occurs by microglia cells by releasing various proteases [59]. There is another main protein that is involved in the pathogenesis of AD is tau whose hyperphosphorylation causes neuronal death of about 3-4 times higher as compared to the AD patient's brain present in the mature neurons and is a major Microtubule-associated protein. Clinically these conditions are known as tauopathies that mainly involves frontotemporal dementia, Parkinsonism linked to chromosome 17, Pick disease, corticobasal degeneration, dementia pugilistica, and progressive supranuclear palsy. Tau protein helps to maintain the stability of the microtubule by interacting with the tubulin protein. Tau protein is abnormally hyperphosphorylated during the disease process which further causes the degeneration of neurons. It has been estimated that about 40% of the AD brain is filled with the abnormal hyperphosphorylation of the tau proteins [60].

6. Pharmacotherapeutic treatments (AD)

Various therapeutic approaches have been introduced into the market for the treatment of Alzheimer's Disease. Based on its pathogenesis various drugs have been developed that target different parameters. As there is a decrease in the neurotransmitter acetylcholine level in the brain therefore various acetylcholinesterase inhibitors have been developed for diagnostic purposes which include Rivastigmine, Galantamine, Donepezil, Memantine, and a combination of Memantine as well as donepezil. Tacrine inhibits both acetylcholinesterases as well as butyrylcholinesterase. The inhibition of these enzymes may be reversible, irreversible as well as pseudo reversible. Various categories of drug agents are used for the treatment of Alzheimer's which include Anti-cholinesterase, Glutamate receptor antagonists, muscarinic agonists, Anti-inflammatory drugs, Chelating agents, Oestrogens, Anti-oxidants, and secretase inhibitors. Different agents show their effects according to different mechanisms. Galantamine is another drug that has anticholinesterase activity. It is highly efficacious as it has all competitive, reversible activity for acetylcholinesterase [61].

Other than this there is another class of agents that involves muscarinic receptor agonistic effects such as bethacholine, arecholine, and pilocarpine. The second generation of drugs was mainly discovered to treat specifically AD which has an agonistic activity e.g. milameline, and xanomeline. Glutamate receptor antagonist is another category that is also used as AD therapy. Glutamate is known for causing excitatory activity. Excessive activation of the receptors by glutamate shown to have a helpful effect in the case of various neurodegenerative disorders [62]. Accumulation of various chelating agents into the brain is also used

significantly for treatment purposes which causes the accumulation of senile plaques. These agents reduce the concentration of zinc and copper in the brain of AD patients which helps in the cognition-enhancing effect. There are several experimental studies which have been done over the past many years to develop some new drugs for the treatment of AD which mainly inhibit the accumulation of Aβ in the brain, various inflammatory responses needed to be reduced [63]

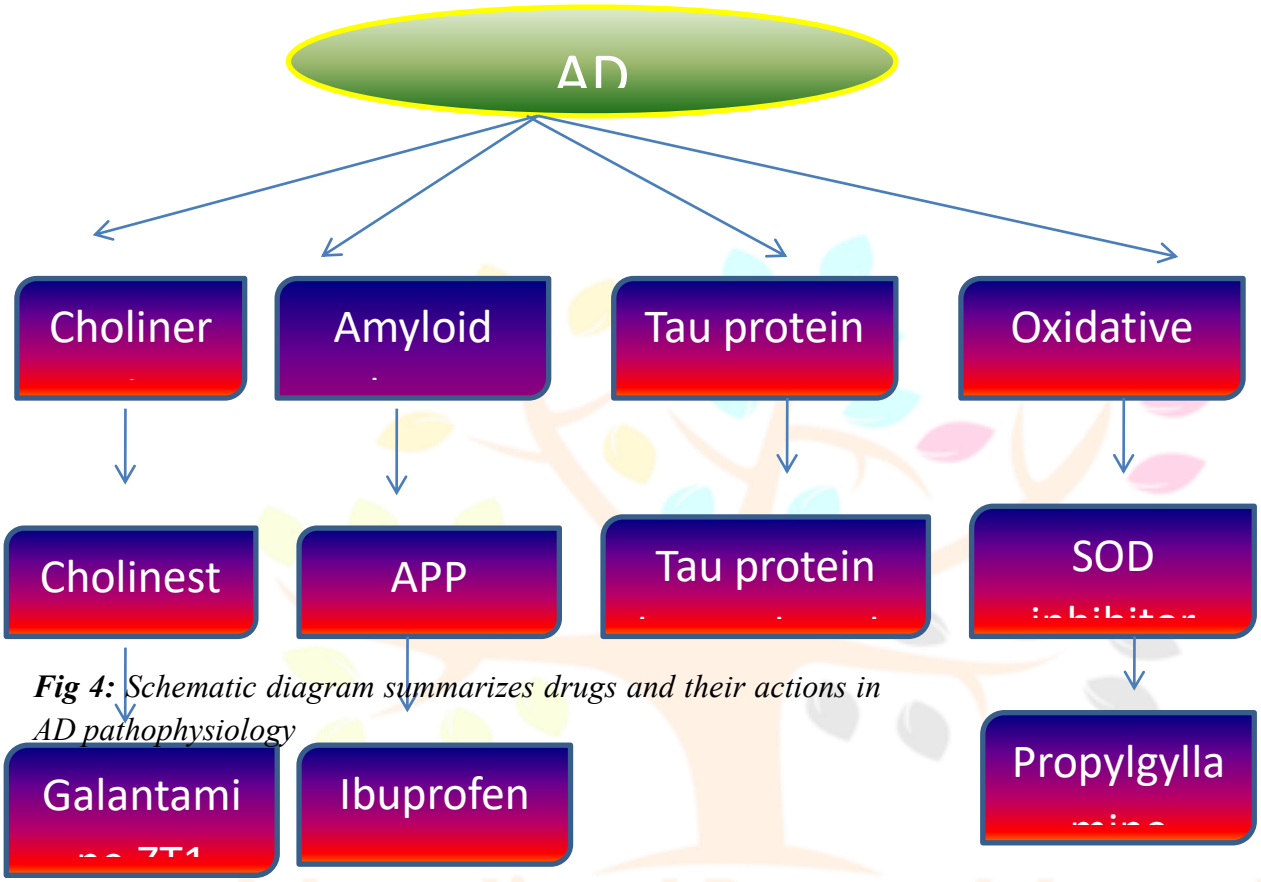

Fig 4: *Schematic diagram summarizes drugs and their actions in AD pathophysiology*

7. Drugs act by a dual mechanism in the case of AD

There are various other agents which have a dual mechanism of action e.g. Galantamine. It has anticholinesterase as well as action on nicotinic acetylcholine receptors (nAchRs) [64]. One other drug Propargyllamine has shown its effect to treat AD by acting on multiple pathways. It has anti-oxidant activity by inhibiting the Superoxide dismutase. It also acts as an MAO inhibitor. It has shown the neuroprotective effect by inhibiting apoptosis (BAX, BAD) gene inhibitors. Overall it has been shown to inhibit amyloid production which helps to decrease AD progression [65]. There are various NSAIDs also which has shown anti-inflammatory activity in the mouse model of AD (APP transgenic mouse model). These compounds mainly inhibit amyloid plaque deposition e.g. Ibuprofen. Ibuprofen has shown both anti-inflammatory as well as amyloid-lowering activity [66].

8. Limitations of the AD mouse model

There are several limitations associated with Alzheimer's disease animal models. It has been found that it is not as complex as compared to human physiology due to the lack of complex interaction between pharmacokinetics and pharmacodynamics with physiology. This model does not reflect the actual condition of AD in humans. There is a lack of pathological characteristics of Alzheimer's disease such as tangles or plaque morphology and solubility characteristics. So overall there are several lack points associated with Alzheimer's disease mouse model [68]. Another major limitation associated with Alzheimer's disease mouse model is targeting the amyloid hypothesis. It is not a very effective pathway to treat AD. The tau pathway has been shown more effective for AD physiology [69].

9. Limitation of clinical trials

Trials conducted for AD are found to failed several times. The duration of AD clinical trials is found to be longer and the frequency of the site visit is also found to be more. It causes a huge burden for elderly patients and their caregivers hence the difficulty in conducting the trial. Another major issue associated with AD clinical trials is difficulty in the enrollment of the targeted population. There are many inclusion criteria for the enrollment of the targeted population i.e. only patients who are suffering from the disease should be enrolled which are most often defined by the range of scores on mini-mental scale examination.

Financial limitation:

It was found that 22% of the net failed studies in the phase 3 studies were mainly due to financial reasons. There were more requirements for staff members, storage facilities, some necessary infrastructure, and financial outlay. Undefunding caused lesser enrolment of subjects that were necessary for concluding statistical modeling [70].

Creative and Construct validity: Many errors caused the lack of translation potential of preclinical data of Alzheimer's disease into the clinical data. Two types of an error lead to such problems extrinsic error and intrinsic error. Intrinsic errors are further of two different types which include systemic error and random error. The systemic error which is caused systematically throughout the procedure due to wrong measurement through the instrument or instrument causes inaccuracy in the method. Random is caused by using the wrong methodology or wrong method to perform the procedure. Inaccuracy and imprecision while experimenting. Another category of error is an extrinsic error which includes various patient factors, inappropriate study design, and using the wrong drug. Various factors which lead to such effects are serious inaccuracies, imprecision biases, and compromises in the study protocol [34].

Various other factors: Innate complexity and constituent pathology lead to the failure of most CTs. Huge challenge to identify the underlying molecular mechanism of the disease. Many pathological pathways

involved in AD still need to be discovered. Alzheimer's disease associated with several other co-morbid conditions makes its pathophysiology more complex. There occurs suboptimal study design (lack and/or inadequate biomarkers outcome measurements). The time course of treatment in relation to the development of the disease is very short [71].

List of variables causes lack of translation potential of data for AD: There are various variables or factors which cause huge problems in Alzheimer's disease research. Such factors include food supplements taken by the patient which leads to the progression of the disease, mental exertion such as trauma, stress, disturbance in the sleep-wake cycle, education, occupational fulfillment, leisure participation, multilingualism, concomitant illness, and unusual medication interaction. These factors cause the repeated failure of promising drug therapies for Alzheimer's disease. Other than this some other reasons which lead to such changes include slow progress in Alzheimer's disease, limited investigation on Amyloid beta, multiple animal models have been discovered but none of them is completely characterized, lack of good laboratory practices in the animal study, gaps in trial design and statistical analysis, lack of translation between scientists and clinicians, no standard treatment has been discovered till now, pathophysiological dissimilarities amount animal and human model [72]

10. Improvement in clinical trial conduct of AD

Various steps need to be taken for improving the conduction of clinical trials in Alzheimer's. It can be done by increasing education and awareness among AD patients as well as their caregivers. Various strategies need to be applied to enhance the recruitment rate by increasing the number of clinical trials as well as the site of clinical trial conduct, clinical trial conduct should be made more easier and convenient [73].

Recommendations

Various steps could be adopted for more improvement in the clinical trials of Alzheimer's disease. Redefining the diagnostic aspects, reevaluation prevailing pathogenic models, advanced guidelines for treatments and management of Alzheimer's disease, and more emphasis on drug research and development could make a difference in the Alzheimer's disease clinical trial and disease management. At the same time, the introduction of pharmacogenomics could make a revolution. It can help a lot in improving the development of advanced level more effective drugs and personalized treatments. More awareness of preventive programs could help reduce Alzheimer's disease.

Eligible candidates in this realm should get timely information for participation in trials. They should be given all the necessary infrastructure. The number of trial sites could be increased [71].

Table 2: Summary of different clinical trials in Alzheimer's disease

Intervention	Phase	Clinical trials.gov identifier	Status	No. of participants	Results
Insulin	Phase I	NCT00581867	Completed	29	Serious adverse event Death-0/29
Florbetapir	PhaseII	NCT01662882	Completed	48	No adverse events found
Memantine Placebo	Phase IV	NCT00933608	Completed	17	Serious adverse event-1/7 (Memantine) Nonserious adverse event-(3/7)
Minocycline	PhaseII	NCT01463384	Completed	13	No serious adverse effects were found
Florbetapir- F18	Phase II	NCT00702143	Completed	184	Serious adverse event 1/184 Nonserious adverse event-2/184
.....MK-6240	Phase1	NCT02562989	Completed	13	No serious adverse events found
.....CNP520 .....Placebo	Phase2	NCT02576639	Completed	124	Serious adverse events:1/26 of CNP520 (35mg)
.....[11C]MK-6884	Phase 1	NCT02621606	Completed	20	Serious adverse event (tendon rupture)-1/7
.....[18F] .....Flutemetamol	Phase2	NCT02813070	Completed	70	No serious adverse effects
.....Ginkgo biloba, ... Placebo	Phase3	NCT00010803	Completed	3069	Serious adverse event :961/1524 Other adverse effects:1504/1545
Levetiracetam 62.5mg,	Phase2	NCT01044758	Completed	96	No serious adverse effects

.....Levetiracetam .....125mg, Levetiracetam ..... 250mg, Placebo					
Citalopram, . Placebo	Phase3	NCT00898807	Completed	186	Serious adverse events 8/94
Bexarotene	Phase2	NCT01782742	Completed	20	No serious adverse effect
Acitretin, ...Placebo	Phase2	NCT01078168	Completed	22	Serious adverse event 1/11
Donepezil	Phase4	NCT00381381	Completed	199	Serious adverse events:4/199
MK-0249	Phase 1	NCT00874939	Terminated	-	The study terminated before randomization and treatment.
Bryostatin1	Phase 1	NCT02221947	Terminated	. -	Part 2 of the study is replaced by NTRP-101-202, assessing 3 doses of bryostatin
LY2886721	Phase 1	NCT01561430	Terminated	-	The study terminated due to abnormal liver biochemical tests in some patients.
TRx0237	Phase2	NCT01626391	Terminated		The study was terminated due to administrative reasons.
Dimebon	Phase3	NCT00912288	Terminated	-	Results are not summarized because of the early termination of the study due to modification in the development plan of the study medication

					following the lack of demonstration of efficacy in the completed DIM14, Anemia, Cardiomyopathy, Pneumonia, UTI, and encephalopathy reported.
Memantine	Phase3	NCT00857649	Terminated	-	Long recruitment, premature termination, substantial protocol changes; baseline imbalances (concomitant medication and severity of agitation).

11. Conclusion

As has been surveyed various promising therapies have been developed for the treatment of AD but these are found to be infrequently failed continuously. Various parameters are involved in this failure of clinical trials for AD. There are two categories of variables that are involved in the disruption of the clinical trial in AD. These variables are mainly involved in our everyday activities e.g. diet, education, mental exertion, leisure participation, multilingualism, sleep, and trauma. Other categories of variables involved clinically are environment, family, coaching, various medication, and illness To summarize the overall factors affecting the AD clinical trial are slow to progress diagnosis of AD, no availability of standard treatment therapy, limited investigation on Aβ and other pathologies, multiple animal models but none well characterized, pathophysiological dissimilarities between animal and human model, lack of GLP in animal studies, gaps in trial design and statistical analysis, lack in translation between scientist and clinicians [74]

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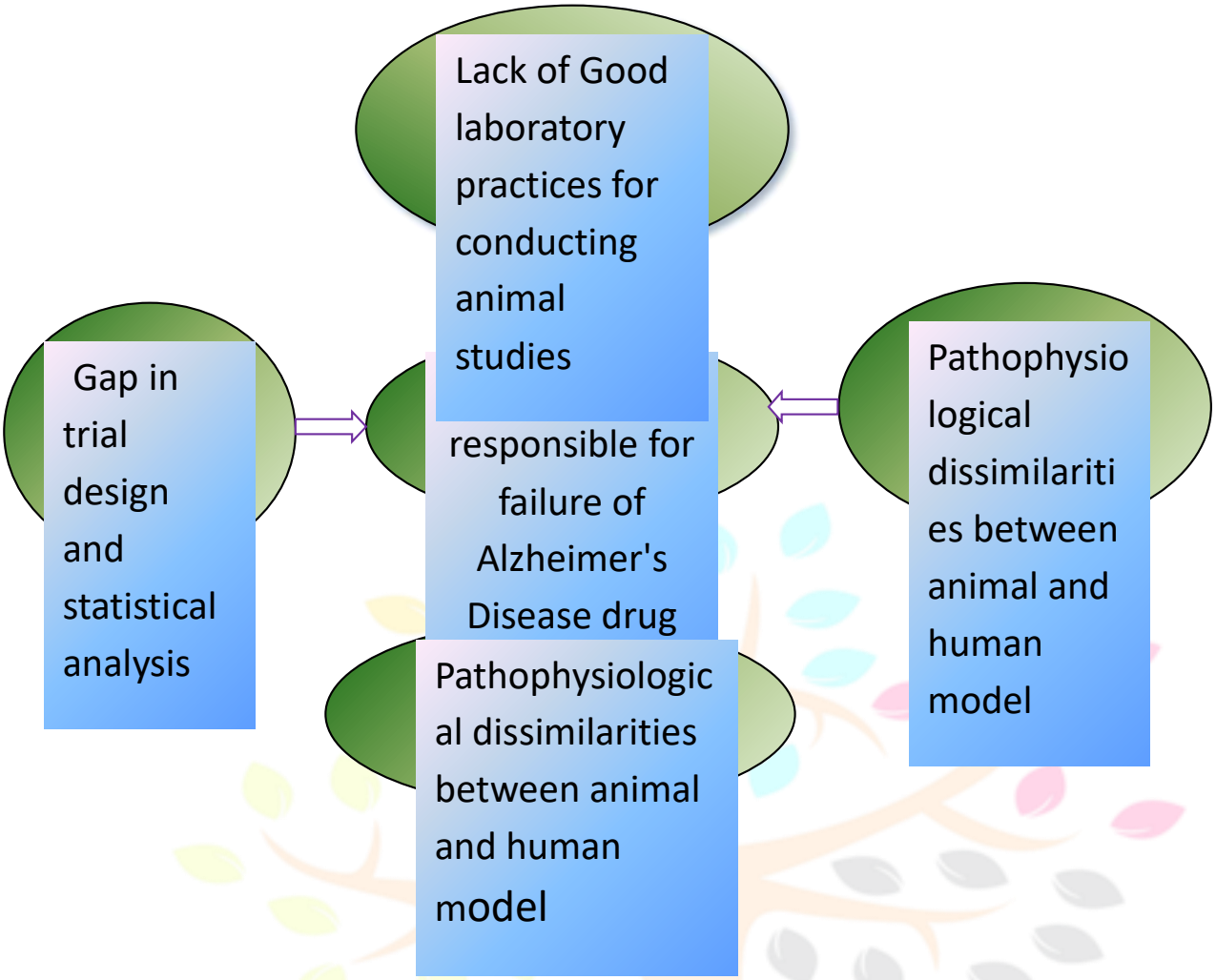

Fig. *Factors responsible for failure of Alzheimer's disease drug therapy*

Consent for Publication

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LIST OF ABBREVIATIONS

AD =Alzheimer's Disease

Aβ =Amyloid beta

AChE= Acetylcholinesterase

ADCT=Alzheimer's Disease Clinical Trial

GLP=Good laboratory practices

FDA=Food and Drug Administration

ApoE=Apolipoprotein E

CA1= Cornu Ammonis

APP=Amyloid Precursor Protein

NSAID=Non Steroidal Anti-inflammatory Drugs

CT=Clinical Trial

MAO-A= Monoamineoxidase

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