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Original Article

Systematic Review on Pathology and Drug Efficacy Clinical Trials (1973-2023) for Cognitive Impairment and Alzheimer's Dementia

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Abstract

Rationale: *The systematic review evaluates the results of last fifty years (1973-2023) of clinical trials on pathology and treatment for cognitive impairment including Alzheimer's dementia (AD dementia).*
Objectives: *Alzheimer's dementia is a growing public health concern worldwide. The systematic review analyzes the disease confirming pathological findings presented by modern imaging techniques MRI/PET. In addition, we analyze the success of fifty years of therapeutic advancements of the neurological disabilities and count on the safe drugs to treat clinical conditions of AD dementia.*
Findings: *We followed the PRISMA guidelines to determine the inclusion and exclusion criteria for the selection of clinical records collected from the NCBI databases. We analyzed the drug efficacy results on the three aspects of the AD brain: (a) morphological deformation of the choroid plexus and hippocampus; (b) senile plaques with amyloid beta42 (Abeta42) including hyperintensities of neurons; and (c) inhibitory action of acetylcholinesterase enzyme. The pathological findings include detection of Abeta42 plaques in cerebral cortex and retention ability of trial drugs in cerebrospinal fluid versus blood plasma of AD patients in the context of disease progression and treatment efficacy. The clinical trial records demonstrated evidence of genetic susceptibility factor(s) clustered in European populations. The susceptibility is also found due to mutations in the presenilin-1 gene and expression of the ApoEε-allele among the population. The clinical records demonstrate moderate efficacy of cholinesterase inhibitors Donepezil and Rivastigmine in improving cognition. The antibodies aducanumab, donanemab, and lecanemab show low to moderate success in removing plaques and reducing plasma Abeta burden.*
Conclusion: *The cholinesterase inhibitors demonstrate moderate success in improving cognition. However, the overall efficacy of antibody treatment was poor. The findings suggest a need for new generation drugs which can clear plaques and improve cognition for AD.*

Introduction

Alzheimer's dementia (AD) is an age-associated multisymptomatic neurological disorder. The susceptibility factors are unknown yet but can be either sporadic or familial or both. The chronic interaction with environmental risk factors like toxic agents, microbial and viral including prion latency in nervous system are critical for the possibility of dementia onset in long run. However, the impact of inherent genetic influences cannot be ruled out. The behavioral outcomes such as aphasia and gradual inability to perform immediate tasks, isolated and depressed personality with aggressive outcome retract the patients from their social environment. This systematic review presented the outcomes of the last fifty years (1973-2023) of clinical trials on AD brain pathology and drugs for treatment of clinical syndromes.

Chronic neuronal dysfunction with gray matter atrophy and white matter hyperintensity in the AD brain begins as early as the age of 45 years and later 60-75 years of age [1-3]. Accumulation of amyloid beta 42 (Aβ42) and tau fibrils aggravates brain pathology in AD with cognitive impairment. Trained caregiver-assistance for AD patients provides initial diagnoses achieved by the Mini Mental State Examination (MMSE) for developing dementia and the AD8 test for preexisting dementia [4,5]. The modern imaging techniques, MRI and PET, exhibit gross anatomical alterations in the cortex, hippocampus, and limbic areas of the AD brain [6]. As found from the outcomes of clinical trials, the central pathology of AD is the formation and deposition of amyloid beta (Aβ) as well as phosphorylation of fibrillar tau protein to form neurofibrillary tangles (NFT). In the long run, Aβ-containing senile plaques

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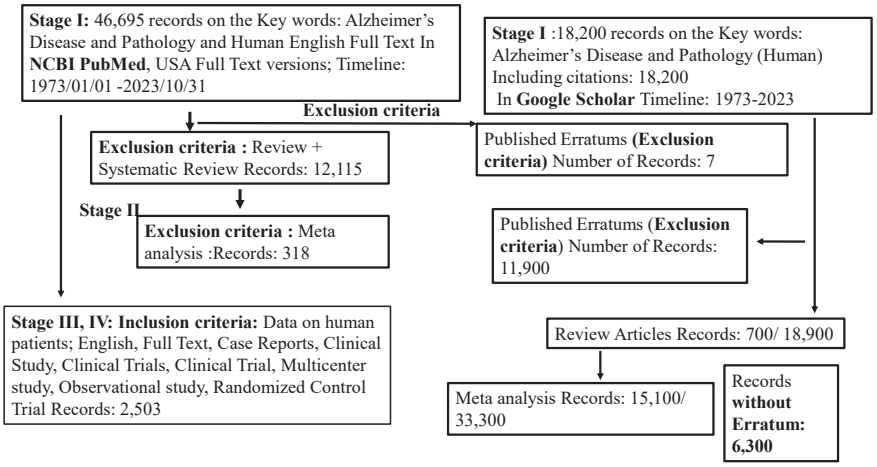

***Figure 1**. Selection of clinical records using key word combination, Alzheimer's Disease and Pathology. The primary filters are English language, Full Text, Human and timeline January 1973 to October 2023 (50 years) in PubMed NCBI. The chart indicates the stages following PRISMA guideline. The Inclusion and Exclusion criteria are mentioned to specify the selection process.*

and NFT alter limbic and frontal cortex spatial orientation [7,8]. In addition, aging process alters choroid plexus function and cerebrospinal fluid turnover, thus promoting neurological disabilities, including neuropsychiatric disorders [9,10].

Methods

Selection of Inclusion and Exclusion parameters for systematic analysis

We followed the PRISMA guidelines (PRISMA Website: http://www.prisma-statement.org) to screen the clinical studies from NCBI, PubMed (End-Note literature search time period: December 20, 2023, to January 14, 2024). We primarily selected 46,695 human, full-text, English-published articles within the timeline of January1973 to October 2023, using the keyword combination: Alzheimer's Disease and Pathology. Then, we sorted the clinical studies on the basis of exclusion and inclusion criteria (Figure 1) to finally select 2,503 clinical articles (the imposed filters to NCBI, PubMed were clinical trials, randomized controlled trials, clinical observations, and reports) for analysis of the results.

The secondary screening of the 2,503 clinical trial studies finally results the selected 719 clinical trials, 304 randomized controlled trials, 578 multicenter studies, 928 clinical studies, 1,164 case reports, and 192 observational studies. We further selected the clinical records from the secondary screened clinical findings on the basis of specific pathological outcome (Table 1). The primary screening of AD dementia drugs availability and treatment has been performed by using the keyword combination Alzheimer's Dementia and Therapy. The search in the NCBI, PubMed, provided 44,097 human, full-text English articles. The inclusion and exclusion criteria (Figure 2) were imposed as mentioned in the Methods section to screen out 3,533 clinical trials and 2,649 randomized controlled trials. Furthermore, we selected the clinical records presenting efficacy of drug treatment under pharmacological and non-pharmacological approaches, thus, predominantly selecting the two major ongoing strategies: acetylcholinesterase inhibitor treatment and antibody therapy (Tables 2 & 3). The higher number of clinical records are compared with the lowest one indicate the addressable clinical concerns in AD patients under the stage of confirmation. The scheme for determining the information following PRISMA guideline for systematic review is presented below:

Stage 1. Identification

A Number of Individual Records identified through database search: Key words ("Alzheimer's Disease and Pathology, "Alzheimer's Dementia and Therapy")

B Number of Identical Records obtained from various sources (using same Key words).

Stage 2. Screening

Total Number of records removed from screened materials (exclusion).

Stage 3. Eligibility (Inclusion)

A. English language

B. Full length articles

C. Results description on Human.

D. Status of the article- accepted to journal, continued.

Stage 4. Included information materials

A Clinical records on mild, moderate-to-severe cognitive impairment, and dementia, as mentioned in published articles. Clinical records of drug treatment were also included in the systematic review.

B Time period: January 1, 1973- October 31, 2023.

Statistics

F-test two samples for variances is used to determine range of F and F critical values for significant number of published clinical records and/or number of patients enrolled as mentioned in the clinical records (p-value).

Results

Clinical outcomes of AD brain

Accumulation of Amyloid beta generating senile plaque caused Alzheimer's disease (AD). We found the highest number of clinical records, n=275 (Clinical Trials, Randomized Controlled Trials, Clinical Study, Multicenter Study, Case Reports and Observational Study) demonstrate presence of senile plaques in AD patients' brain. We keep the number of records for senile plaques as control and compared the number of clinical records

Table 1. *†Selection of clinical records on Alzheimer's Disease Pathology*

Selected AD pathology	Number of Clinical Trial	Number of Randomized Controlled trial	Number of Clinical study	Number of Multi center study	Number of Case report	Number of Observational study	Total Clinical findings on AD Pathology	F-test two samples for variances
†Senile plaque	47	19	53	41	109	6	275	-
Cytoskeleton	24	2	30	19	162	4	241	p>0.05
SNAP 25 Accumulation	0	0	0	0	2	0	2	p<0.05
Aβ deposition-MRI/ PET records	24	9	38	12	50	12	145	p>0.05
Tau deposition- MRI/ PET Imaging results	12	4	25	13	67	12	133	p>0.05
Degenerating neuron	24	6	27	17	112	2	188	p>0.05
Cerebrovascular atrophy	17	5	23	18	16	6	85	p<0.05
Gray matter atrophy	22	5	31	21	6	9	94	p<0.05
White Matter atrophy	23	9	39	38	33	15	158	p>0.05
White matter hyperintensity	26	11	41	44	10	14	146	p≥0.05
Brain atrophy fronto-temporal dementia	10	2	15	20	76	4	127	p>0.05
Neurofibril	21	1	24	16	157	3	222	p>0.05
Accumulation of Copper	2	1	3	0	7	1	14	p<0.05
Accumulation of Zinc	2	1	2	1	2	1	9	p<0.05
Accumulation of Iron	7	2	8	1	16	1	34	p<0.05
Accumulation of Aluminum	2	1	2	0	5	0	10	p<0.05
Hippocampus head volume	7	1	8	2	10	1	29	p<0.05
Extracellular matrix	1	0	0	0	0	0	1	p<0.05
TDP-43	2	1	3	4	55	1	66	p<0.05
Heparan sulfate proteoglycan	1	0	0	0	0	0	1	p<0.05
Fibronectin, Tau fibers, Biondi inclusions	4	0	4	0	6	1	15	p<0.05

ǂThe clinical records are selected on the basis of specific brain pathology findings of patients with cognitive impairment and clinical AD and postmortem analysis of AD brains from the primarily screened records.
†We compare the number of clinical records demonstrating brain pathology findings during cognitive impairment and different stages of AD dementia with number of clinical records on senile plaque pathology. The number of records closer to that of the senile plaque clinical records are less significant (p>0.05).

demonstrating other pathological findings in AD brain under various clinical conditions of cognitive impairment (CI) (low, moderate to severe) and AD dementia (AD). The alterations in the cytoskeleton (n=241 clinical records) and associated Tau deposition (detected by MRI/PET) (n=133 clinical records) are presented in the growing numbers of clinical records comparable to the records presenting evidence of senile plaques in AD brain (p>0.05). The noticeable number of clinical records demonstrate MRI/PET brain imaging results on amyloid beta (Aβ) accumulation (n=145 clinical records) during cognitive impairment and AD dementia clinical conditions of patients (Table 1). In comparison, there are no clinical records, but 2 case reports are found for SNAP25 accumulation of which one is selected [11].

There are 188 clinical records (24 clinical trials, 6 randomized controlled trials, 27 clinical studies, 17 multicenter studies, 112 case reports, and 2 observational studies) showing degenerating neurons as critical for symptomatic cognitive impairment and AD brain pathology as compared to senile plaques (p>0.05). We can take a conclusion from the number of clinical records (Table 1) and number of enrolled patients (Normal= 169, CI=672, AD=429 and PD/FTD=41) (Table 4) that degeneration of neurons in CI and AD patients represents AD pathology along with senile plaques.

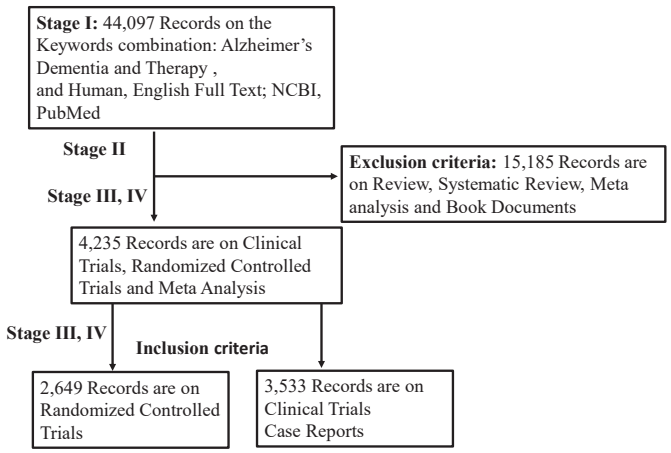

Figure 2. *Selection of clinical records using key word combination, Alzheimer's Dementia and treatment. The primary filters are English language, Full Text, Human and timeline January 1973 to October 2023 (50 years) in PubMed NCBI. The chart indicates the stages following PRISMA guideline. The Inclusion and Exclusion criteria are mentioned to specify the selection process.*

Though, neurodegeneration is also reported in Parkinson's Disease with fronto temporal dementia (FTD).

Cerebrovascular atrophy (85 clinical records) is critical for patients with cognitive impairment and AD; the number clinical records are comparatively less as compared to senile plaque records ($p<0.05$) (Table 1). The clinical records of AD brain pathology demonstrated gray matter atrophy (94 clinical records) in the bilateral frontotemporal cortex, insula, and striatum, along with white matter atrophy in the bilateral corpus callosum and uncinate fasciculus [2,11-13]. Alterations in the gray matter structural covariance networks in AD dementia have been reported through changes in the intrinsic connectivity networks (ICN) [13,14]. In addition, the white matter atrophy (158 clinical records) with neuron hyperintensities (146 clinical records) are critical vascular pathology of the AD brain, which demonstrate swelling neurons with accumulation of inclusion bodies as sign of degeneration. The number of enrolled patients (CI and AD) (Table 4) showed positive for cerebrovascular atrophy with gray and white matter atrophy along with cytoskeletal alteration.

Shrunken hippocampal heads have been demonstrated in the human aging brain, as well as in AD dementia [15]. The number of clinical records is low, but the finding has growing importance in regard to cognitive impairment. The implication of this critical pathology in the AD brain is associated with cerebrovascular atrophy [14,16-18] demonstrating that an

Table 2. *Selected clinical records on cholinesterase inhibitors for cognitive impairment and AD dementia*

Drugs under trial	*Clinical trials records	*Randomized Controlled trials records	Case Reports	Dose range and route	≠ Cognitive impairment -Benefit versus Risk ratio	≠ AD Dementia	F-test two samples for variances
Physostigmine And analog NXX-066	64	35	10	0.004, 0.009, 0.013 mg/ kg body weight; i.m; Single dose: 1-1.5 mg , optimized as 2-12 mg/day for 1 week i.v infusion	poor	Not	-
Donepezil	374	258	106	5-10 mg/ day oral, i.v injection; 20-25 mg dermal patch; 6, 24, 30 weeks	moderate	moderate	$p>0.05$
Rivastigmine (alone and combination with Donepezil); analog NAP226-90	181	115	49	4.6 mg/ day and 13.3 mg/ day dermal patch; 12 mg/ day capsule oral administration	moderate	moderate	$p>0.05$
Galantamine (alone and combination with Donepezil)	135	89	22	8, 16, 24 mg/ day for 12 and 21 weeks by oral or i.v administration	moderate; improves aggression/ agitation condition	moderate	$p>0.05$

* In the second screening process we further screened the primarily selected clinical records using filters : Clinical Trials and Randomized controlled trial, Case Reports and determined the dose ranges and route of treatment, any improvement in cognition (Benefit versus Risk ratio) and efficacy of the drug treatment on AD Dementia. for determining efficacy of currently available drugs for AD dementia. The significant numbers of clinical records for AD drug efficacy are evaluated by comparing the number of clinical records with the number of records screened from Physostigmine (And analog NXX-066) treatment. The F test is used to determine p-value.
≠ The selected AD pathology - Cognitive Impairment and AD dementia are marked to evaluate efficacy of the drugs.

Table 3. *Selection of clinical records on antibody therapy for cognitive impairment and AD dementia*

Antibody therapy‡	Clinical trial	Randomized Controlled trial	Case reports	Dose, Routes	Senile plaque (clinical records)	Abeta	Clinical findings	F-test two samples for variances
Semorinemab (anti-tau antibody)	3	2	0	"4500mg, every 4 weeks for 48 to 60 weeks up to 90 weeks; i.v route"	0	0	"No overall improvement Does not slow down functional decline in AD patients. Safe and well tolerated"	
Donanemab (LY3002813) Anti-amyloid beta antibody)	6	5	0	"Single dose 10-, 20- or 40- mg/kg; multiple doses of 10-mg/kg every 2 weeks for 24 weeks and 10- or 20-mg / kg every 4 weeks for 72 weeks or placebo; i.v. route"	4	1	Reduce brain Amyloid load (PET finding)	p>0.05
Aducanumab (monoclonal IgG1)	8	6	4	"Single dose: 0.3-60 mg/ kg; multiple dose:1, 3, 6, 10 mg/ kg every 4 weeks; i.v route"	2	3	"Reduce brain amyloid burden and moderately reduce cognitive decline (amyloid PET finding);"	p>0.05
Lecanemab	8	7	1	"10 mg/ kg biweekly for 12 and 18 months, i.v route"	0	0	"Moderately slowing down clinical decline; Reduction in plasma amyloid beta 40/42; plasma tau burden;"	p>0.05

‡The number of clinical records indicate the reports on efficacy of antibody treatment. The significance level (p-value) is determined by F-test by comparing the number of records for different antibody treatment with records for Semorinemab (anti-tau antibody) treatment. The p>0.05 indicates larger number of clinical records available for antibody treatment compared to Semorinemab treatment.

altered structure of the choroid plexus correlates with Aβ42 accumulation in the cerebrospinal fluid (CSF). In the context of AD brain pathology, we found the clinical records on neurofibril accumulation (222 clinical records). The neurofibril networks and senile plaques (275 clinical records) are found as markers for cognitive impairment and AD brain pathology (Table 1). The outcomes of these clinical studies indicate the pathological biomarkers other than senile plaque, gray matter atrophy and white matter hyperintensity. This is abnormal anatomy of choroid plexus. The reported biological markers for AD includes presence of Aβ42, phospho-tau, TREM2, ApoE [19]; heparan sulfate proteoglycan, collagen, fibronectin, Biondi inclusions [20,21]. All these are found to accumulate in the CSF of AD brains.

The onset of epilepsy has been found as comorbid risk factors detected in AD patients even earlier than cognitive decline [22,23]. It is noteworthy in regard to the context that chronic brain infection and focal neurodegeneration, inflammation raise the possibility of establishing epileptic neurological conditions. The alterations in brain morphology are critical pathology associated with epilepsy. AD pathology also includes extracellular matrix (ECM) abnormalities associated with glaucoma and early cognitive decline [22,24]. The inflammatory responses have been reported with the expression of Cationic Antimicrobial Protein Mi37 (CAP37) and accumulated Aβ [25].

In the choroid plexus, threads and tangles are associated with Fibronectin and Tau proteins. Identification of these tangled networks in the postmortem AD brains demonstrates that Tau protein constitutes paired helical filaments with negligible alpha or beta conformation [26,27]. Cloning and cDNA sequencing identified the paired helical filament protein as a microtubule-associated protein Tau [28]. Studies on fibrillar protein deposition and AD pathology have demonstrated the impact of paired helical filaments [29].

The accumulation of Abeta42 in senile plaques with neurofibrillary tangles causes cognitive impairment [30]. A study [31] demonstrated that the presence of TDP-43, Lewy bodies, and argyrophilic grains in the amygdala are related to seizures and comorbidity of frontotemporal dementia. Different studies have demonstrated that the accumulation of copper (14 records), zinc (9 records), iron (34 records), and aluminum (10 records) alters Aβ42 fibrillation and deposition. As a matter of fact, these metal ions and membrane lipid bilayer allow a solid phase support to stabilize the deposition of amyloid beta to form plaques. The protein structural conformation and hydrophobicity are two additional biophysical parameters for Abeta accumulation in brain. Though the clinical studies did not mention the tissue/ cellular source(s) of amyloid beta and mechanism of accumulation in brain.

The biomarker for clinical outcome of familial AD includes genetic mutation. We sorted out 115 clinical records showing presence of mutations in the Gamma Secretase components-Presenilin 1 and 2 (PSEN 1 and 2) found in the autosomal dominant AD [32]. The epidemiology based studies [33,34] also demonstrate the involvement of chromosome 17q25 in the European population with novel loci: 10q24 and chr2p21 in relation to AD susceptibility. However, the distinct genetic involvement for AD onset in Asian and African populations is not clear.

Therapeutic interventions for Alzheimer's dementia

Efficacy of Physostigmine

We selected 64 clinical trials, 35 randomized controlled trials and 10 case reports on the efficacy of Physostigmine and analog NXX-066 in patients with cognitive impairment and AD dementia (Table 2). The clinical records have shown that the compound is safe but has a poor outcome in improving dementia. We used the clinical records of Physostigmine treatment as a control for comparison (Table2).

Efficacy of Acetyl cholinesterase inhibitors Donepezil, Rivastigmine and Galantamine

We selected 374 clinical trials, 258 randomized controlled trials, and 106 case reports on the efficacy of Donepezil treatment for mild to moderate cognitive impairment and dementia (larger number of clinical records as compared with Physostigmine treatment trials; $p>0.05$). A randomized controlled trial [35] demonstrated higher donepezil concentration in CSF following 24- hour interval than a 12-hour interval of treatment (10 mg per day for three months prior to sample collection). Donepezil treatment reduces basal forebrain atrophy (BFCS) and restores memory function [36]. Donepezil increases CSF-acetylcholinesterase in AD patients [37]. The dose responses of Donepezil have been studied in the presence or absence of a placebo [38]. Rogers and Friedhoff LT [39] demonstrated a linear dose-responsive plasma concentration of Donepezil in healthy volunteers. Donepezil is also effective in improving the clinical conditions of Lewy body dementia [40] and mild to moderate AD dementia with or without any cerebrovascular abnormalities [41]. There is a clinical study [42] demonstrated variations in the efficacy of Donepezil and Rivastigmine in the frontal, temporal, and parietal cortices of the human brain. The clinical findings suggest Donepezil treatment in AD shows better outcome than neuroleptic treatment using antipsychotic drugs [43].

It has been found in the clinical study that Donepezil treatment cannot cause marked decrease in overall and right hippocampal volume as compared with placebo following 24 weeks or less of treatment schedule [44]. The efficacy and safety examination in clinical trial studies demonstrated low to insignificant differences in Donepezil treatment (5 mg/day for forty-two days) with placebo during the primary treatment period of AD dementia [45]. The studies have shown the efficacy of Donepezil on apathy, irritability, emotional activities, depression, and verbal function in elderly AD patients [46]. A clinical trial reported similar efficacy of Donepezil, Rivastigmine and Galantamine in patients compared with untreated controls [47]. Donepezil treatment has been found to be effective for mild AD clinical conditions [48-51]. A study [52] demonstrated a difference in Donepezil action in regard to cortical electroencephalographic (EEG) rhythmicity in patients who responded to treatment. A study [53] also demonstrated the impact of CSF versus plasma levels of acetylcholinesterase activity during long-term treatment with donepezil.

Single-dose Donepezil oral treatment (3 mg) to sixteen patients with diffuse axonal injury [54] demonstrated a beneficial effect on motor cortex excitability by improving short-latency afferent inhibition. The study [55] demonstrated that a single dose (5 mg) of Donepezil improves neurophysiological measures of spatial working memory and error monitoring tests (Groton Maze Learning Test) in healthy and older adults with and without AD; 3 – 6 hour post dosing). A clinical trial demonstrates the IC50 of

Table 4. *Number of patients enrolled in the clinical and randomized controlled trials (1973-2023) to identify Alzheimer's disease brain pathology*

Selected AD Pathology	Number of patients in Clinical and Randomized Controlled trials				F-test two samples- number of patients with Cytoskeletal change
	Normal	CI†	AD††	PD/FTD‡	
Cytoskeleton	85	598	822	-	-
Aβ-deposition: MRI/PET records*	368	903	655	-	0.5>p≥0.05
Degenerating neurons	169	672	429	50	0.5>p≥0.05
Cerebrovascular atrophy‡	189	263	1480	41	0.5>p≥0.05
Gray Matter atrophy	696	629	501	98	0.5>p≥0.05
White Matter atrophy‡	58	1457	1640	-	0.5>p≥0.05
White matter hyperintensity‡	121	2291	2795	-	0.5>p≥0.05
Neurofibril	16	-	715	-	0.5>p≥0.05
Senile plaques*	393	219	1133	-	0.5>p≥0.05
Significance F-test two samples- pathological evidence wrt Normal Control	-	0.5>p≥0.05	0.5>p≥0.05		

The number of patients selected in the clinical and randomized control trials are presented for each mentioned pathology identified in cognitive impairment (CI†) (mild, moderate, severe) and Alzheimer's disease (AD††) (mild to severe) leading dementia. The pathology like degenerating neuron, cerebrovascular atrophy, gray matter atrophy are found in Parkinson's disease with fronto-temporal dementia (PD/FTD ‡).

‡Number of patients with cerebrovascular atrophy, gray and white matter atrophy, white matter hyperintensity are also diagnosed for other brain pathologies like cytoskeletal change, presence of neurofibrils and degenerating neurons ($0.5>p\geq 0.05$).

*Number of patients with amyloid beta deposition (MRI, PET demonstration) and senile plaques represent clinical Alzheimer's disease are also diagnosed for neurodegeneration as primary events.

The number of patients with pathological identification of cognitive impairment (CI) and clinical Alzheimer's disease are comparable ($p>0.05$).

Table 5. *Number of patients enrolled in the clinical and randomized controlled trials (1973-2023)for determining efficacy of existing drugs for Alzheimer's dementia clinical conditions.*

Existing AD drugs under trial‡	Number of patients enrolled in Clinical/Randomized Controlled trials with variable symptoms under treatment			MMSE/ADAS-Cog/SIB	Mood/Anxiety/ Depression	Gait	Degradation of Amyloid plaque	Safety/ side effect
	Normal/ Placebo	CI†	AD‡					
Physostigmine alone and NXX- 066 analog	-	-	17	No	No	No	-	Safe
Donepezil alone and combination with other drugs	-	-	16,223 and more	Improve alone and combination	Improve alone and combination	-	-	Low side effect on long use
Rivastigmine alone and combination with other drugs	-	-	12,185 and more	Improve alone and combination	Improve	Improve	-	Low side effect on long use
Galantamine alone and combination with other drugs	-	-	9,710 and more	Improve	Improve	Improve	-	Low side effect on long use
Semorinemab	-	-	1,046	No	No	No	No	-
Donanemab (LY3002813)	-	-	590	Improve	-	-	Yes	Moderate
Aducanumab	-	-	6.57	Low to moderate improvement	-	-	Yes	Moderate
Lecanemab	897	-	1754	Low to moderate improvement	-	-	Yes	Moderate

‡ The existing drugs are approved by FDA for treatment of Alzheimer's disease various clinical conditions – low, moderate to severe cognitive impairment (CI†) and AD dementia (AD‡). The Clinical trials enrolled all confirmed or probable AD patients at various stages of CI and AD dementia.

plasma concentration of Donepezil (5 mg/ day for 5.3 months) found 53.6 +/- 4.0 ng/ ml in sixteen possible AD patients [56]. An improvement in dementia was noted in the patient group treated for a short term with Donepezil in combination with cognitive stimulation [57]. The efficacy of treatment has been reported to be higher than that of acetylcholinesterase activity in the AD brain [58].

A Randomized Controlled trial demonstrated the beneficial effects of Donepezil (5 or 10 mg) for 24 weeks in patients with Parkinson's Disease dementia patients [59]. The treatment with a higher dose (23 mg/day over 10 mg/day for 24 weeks) in AD patients showed cognitive improvement compared to the extent of disease severity [60]. A long-term treatment trial has been reported with the effect of Donepezil on ApoE ε4 status, odor detection difficulty, and entorhinal/hippocampus atrophy with depression and cognitive impairment [61]. The improvement in the route of Donepezil administration has been demonstrated recently using the dermal patch delivery method [62] for slow and continuous release.

Oral administration of Rivastigmine demonstrated moderate improvement in cognition in patients with early AD (181 clinical trials, 115 randomized controlled trials, 49 case reports) (Table 2). Galantamine improved cognition, aggressive and agitated behavioral conditions (135 clinical trials, 89 randomized controlled trials, and 22 case reports).

Efficacy of antibody therapy

We found a clinical report demonstrating the diagnostic importance of the antibodies for detecting amyloids and tau [63]. A clinical trial demonstrated that treatment with 5 mg/ day antibody for 30 days increased Amyloid Precursor Protein (APP) in the platelets of patients with mild to moderate AD [64]. Monthly injection of IgG for six months demonstrates a decrease in Aβ42 in the CSF and serum of AD patients [65,66]. Intravenous infusion of monoclonal antibodies has been shown to increase Mini Mental State Examination (MMSE) scores in AD patients with improved cognition abilities [67]. The selected clinical records and outcome of antibody treatment are presented in the Table 3.

The antibodies Donanemab [68,69], Aducanumab [70-72], CrenezumAb [73] and Lecanemab [74] have been demonstrated to reduce Aβ plaques. The antibody drug Semorinemab is found safe but has no efficacy to improve cognitive impairment and AD dementia clinical conditions (Table 3). The number AD patients enrolled for clinical trial is less (Table 5). The limited success of antibody treatment for AD pathology is found from antibody Donanemab treatment to AD patients. Donanemab treatment can reduce the plasma biomarker pTau217. The selected number of clinical and randomized controlled trials (Table 3) demonstrates efficacy of Donanemab treatment through dermal patch as well as i.v routes (Table 3) can moderately reduce senile plaques (brain amyloid).

The large number of enrolled AD patients (n= 16,223, Table 5) in clinical and randomized controlled trials show improvement of MMSE/ADAS-Cog/SIB for cognitive impairment and AD dementia condition. Donanemab moderately improves mood (anxiety/ depression) and gait of enrolled patients and Lecanemab (an IgG1 monoclonal antibody) is less responsive to cognitive improvement. Though, all these antibodies induced brain edema and vomiting tendency as an adverse side effect. The clinical records on Aducanumab treatment (n=18) also demonstrate reduction of accumulated brain amyloid (Table 3). The enrolled 6,570 and more AD patients show low to moderate improvement during Aducanumab treatment; it lowers the accumulated amyloid burden and moderately improves cognition. The clinical records on Lecanemab treatment (Table 3) demonstrate moderate slowing down of cognitive impairment and reduce plasma amyloid beta, tau burden in AD patients (Table 3). The number of patients (n= 1754 AD, n= 897 placebo) enrolled in clinical trials demonstrate low to moderate efficacy of Lecanemab to improve cognition (Table 5). The clinical records (Table 3) and number of enrolled AD patients (Table 5) are growing which demonstrate improved efficacy of cholinesterase drugs and antibody therapy to minimize pathological conditions for cognition and degrade senile plaques.

Discussion

The systematic review presents selected clinical records of AD pathology related to dementia conditions (Table 1) and number of enrolled patients demonstrated brain pathology – senile plaques, neuron degeneration, white matter hyperintensities with atrophy, gray matter atrophy (Table 4). The existing therapeutic interventions (clinical records: Table 2,3) show low to poor efficacy to prevent clinical conditions of AD dementia. However, moderate improvement of cognition results following treatment with acetyl cholinesterase inhibitors, Donepezil, Rivastigmine and Galantamine. The noticeable point is AD treatment procedure has considerable side effects. The higher doses of acetylcholinesterase inhibitor(s) cause side effects possibly due to patients' pre-existing conditions, ability to withstand (or accept) treatment, and age. Thus, as a general rule, titration of the proper dose according to patient age with body weight and route of administration is a critical factor for effective therapy.

Anti-amyloid beta antibody treatment though demonstrates moderate improvement of clinical condition (Tables 3 & 5), the drugs and treatment procedures require thorough improvement as to avoid side effects, such as headache, nausea, and altered vision.

The route of administration and optimum dose of drug(s) for AD treatment are the most critical aspects to evaluate effective therapeutic interventions. The efficacy of the treatment schedule depends on the transport of bioactive compounds through blood brain barrier to a definite location in the cerebrum and limbic areas. In addition, successful treatment depends on the delivery of the drugs to the choroid plexus and intracranial circulation by CSF streaming in the AD brain. Clinical trials have demonstrated that the drug concentration level is lower in the CSF than in plasma. However, a higher concentration of drug in the CSF corresponds to an improvement in cognitive impairment in patients with AD.

In the contemporary timeline as defined in this systematic review analysis, different groups of researchers [75,76] reported overexpression of amyloid precursor protein (APP) due to dysregulation of the human APP gene and due to specialized alternate splicing of human APP mRNA which in turn initiate generation of amyloid beta protein accumulating in neurons for long periods of time. The treatment procedure for these clinical conditions is not developed yet.

Our analysis on the clinical records shows successful drug development should consider the brain pathological findings on (a) morphological deformation of the choroid plexus and hippocampus; (b) senile plaques with amyloid beta42 (Abeta42) including hyperintensities of neurons; and (c) action of acetylcholinesterase enzyme. On the basis of this scale, we found moderate success of the therapy using existing AD drugs. Moreover, the factors like doses and body weight including age of AD patient(s), drug concentration in CSF versus plasma, clearance of amyloid plaque immune complex/ debris from brain, optimum synaptic transmission and concentration of acetylcholine in synapse with respect to activity of cholinesterase enzyme in brain play critical role in overall therapeutic success for Alzheimer's dementia.

Conclusion

The results obtained from the clinical records suggest a moderate level of success in treatment of AD patients with side effects. The clinical findings suggest a need to identify sporadic and genetic risk factors responsible for AD dementia and cognitive impairment. The improvement of the existing treatment by combination therapy and search for new compound(s) as effective AD drugs are two strategic option to prevent brain pathology for AD dementia.

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Conflicts of Interests

Authors do not have any conflicts of interests.

Availability of data and material

The data in the form of tables and figures for this systematic review manuscript are available from the corresponding author (S. D. G.).

Ethics Approval

Not required.

Author Contributions

S.D.G was responsible for the selection of clinical records, examination of all records, extraction of results, and writing of the manuscript. M.B. is an expert in the neuroanatomy of the human brain. M.B. provided critical suggestions and was responsible for formatting the manuscript. Both S.D.G and M.B. have reviewed the final form of the manuscript. Ms Nina Villa (N.V) is a senior medical student at Saint James School of Medicine, ParkRidge, IL campus. She is also a former student of S.D.G.

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