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Cholinesterase inhibitors and non-steroidal anti-inflammatory drugs as Alzheimer's disease therapies: an updated umbrella review of systematic reviews and meta-analyses

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Abstract. – OBJECTIVE: Alzheimer's Disease (AD) is a major neurological disorder marked by an amyloid-beta plaque and neurofibrillary tau-tangle depositions in the brain. Cognitive dysfunction is the key manifestation of AD. In this study, we conducted an umbrella review of meta-analyses on the risk factors and therapeutics targeting cognitive impairment and AD.

MATERIALS AND METHODS: We searched PubMed from January 2000-August, 2016, and screened systematic reviews and meta-analyses of studies that examined the effects of cholinesterase inhibitors in AD patients. We also included studies on non-steroidal anti-inflammatory drugs and AD. The studies comprised meta-analyses of randomized controlled trials and prospective cohorts, with 95% confidence interval. We considered the heterogeneity between different studies, denoted by I2.

RESULTS: We scanned a total of 750 novel meta-analyses on the topics, "risk factors for AD" and "cholinesterase inhibitors and NSAIDs" that target the disease. The search yielded three relevant studies on risk factors, and seven and three studies for ChEIs and NSAIDs respectively. A thorough examination of the studies reinforced the therapeutic role of ChEIs in AD. A combination of the glutamatergic inhibitor, memantine, with ChEIs also proved effective in ameliorating AD progression and occurrence. Contradicting the observational studies, therapeutic role of NSAIDs in AD seemed uncertain. Nonetheless, the studies showed variability in the severity of dementia and number of patient trials. Hence, we claim the need for detailed meta-analyses and superior-quality cohort studies on a larger patient population of AD.

CONCLUSIONS: Overall, our umbrella systematic review offers a unique and immensely helpful resource for researchers and clinicians in the field of AD, and identifies vital research gaps as well.

Key Words:
Risk factors, Alzheimer's Disease, ChEI, Memantine, NSAID, Therapy.

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by manifestations of forgetfulness, cognitive impairment, behavioural changes, confusion, language trouble and thinking inability[1]. If left untreated, symptoms of AD worsen with time, impeding the day-to-day normal functioning of the patient[1]. It has been claimed by the AD-International that more than 30 million people worldwide are victims of dementia, and the prevalence of AD is 60-80%[2]. More than 5 million Americans are reported to be living with AD[3], and in Japan, around 15% of the >65-year-old population suffers from AD[4,5]. AD is also emerging as a major threat to the developing countries, accounting for about 58% of the total population, and is speculated to escalate to about 70% by 2050[6].

The key pathological hallmarks of AD are amyloid beta (Aβ) plaques and neurofibrillary tangles (NFT) that accumulate in the gaps between nerve cells and synaptic junctions[7]. The Aβ and NFTs are generally deposited within the brain hippocampus, the site for memory and cognition, thereby impairing neuronal communication and resulting in neuronal cell death[8-10]. The major risk factors for AD comprise growing age and family history[11-13]. While aging accounts for more than 95% of AD cases, familial AD forms around 2-3% of all cases and demonstra-

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tes AD-like manifestations at an early age[14,15]. The genetic factors, particularly Apolipoprotein, APOE-e4 gene, have an immense impact and markedly increase the risk for AD pathogenesis[16,17]. Additionally, the deregulated processing of amyloid precursor protein, which causes a shift towards the amyloidogenic pathway rather than the non-amyloidogenic, is a major cause for Aβ generation[18].

Altered expression of the neurotransmitters, especially acetylcholine and N-methyl-D-aspartate (NMDA), and neuro-inflammation are major mechanisms inducing AD pathogenesis[19,20]. Hence, cholinesterase inhibitors (ChEIs) and drugs targeting the NMDA receptor, and the non-steroidal anti-inflammatory drugs (NSAID) are usually used to attenuate the progression of AD[21-23]. Anti-amyloid agents that reduce inflammation, oxidative stress, hypercholesterolaemia and cholinergic dysfunction are known to block Aβ generation and aggregation[24]. Drugs that promote cholinergic neurotransmission are also useful in attenuating AD pathogenesis[25]. These agents may reduce apoptosis in the hippocampal neurons, and thereby inhibit AD progression[26]. Enhanced functioning of growth factors and neurotrophins that function via the tropomyosin receptor kinase A contribute in protecting against AD-induced neuronal damage[27].

Some documented research studies[21-23] are available that demonstrate the role of neurotransmitters and inflammation in AD. Cholinergic neuromodulators, such as tacrine, donepezil, rivastigmine and galantamine, NMDA-receptor antagonist, memantine (MEM), and NSAIDs have also been reported to affect AD pathogenesis. Additionally, systematic review and meta-analyses[28,29] on the effects of the therapeutics on AD features, particularly cognitive impairments, have been carried out. However, to the best of knowledge, an umbrella review of the systematic reviews and meta-analyses of AD risk factors and targeted therapies has not been done so far. In the current study, we performed a systematic overview of meta-analyses and an exploratory collective analysis of previous meta-analyses to assess the risk factors of AD and the effects of neurotransmitter modulators and NSAIDs in AD pathology.

Umbrella Meta-analysis Design

The central cholinergic system significantly regulates cognition and learning-memory performances[30]. One of the major pathological features of AD is the damaged cholinergic neurons, resulting in decreased neuronal choline levels[30]. Thus, drugs inhibiting the functions of acetylcholinesterase enzyme that degrades acetylcholine neurotransmitter are clinically used for attenuating AD pathology[31]. The main therapies that attenuate AD symptoms include cholinesterase inhibitors (ChEIs), donepezil, galantamine and rivastigmine and the NMDA receptor antagonist, MEM, or their combinations[32,33]. Meta-analysis studies showed the combination therapy of MEM and donepezil to be quite effective in treating moderate to severe stages of AD[34,35]. However, there have been contradictions in this concept, and several studies hardly claimed any difference between the ChEI+MEM-treated patients and placebo examined through the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog; Rosen et al[36]) or the standardized Mini-Mental State Examination (SMMSE; Molloy and Standish, 1997)[35]. Similarly, meta-analysis studies that determined the relation between classical NSAIDs and AD appeared to have contradictions as well. While few scores failed to show any impact of NSAID treatment, several others demonstrated an association[28,37,38]. Thus, heterogeneity in the results demanded the need for an umbrella review and meta-analysis that include all these meta-analyses. Hence, the present systematic review and meta-analysis included the data on modifiable risk factors for AD. It comprised results obtained from cognitive assessments following treatments with the cholinesterase inhibitors, NMDA receptor antagonists and NSAIDs in AD. The methods of assessment mainly included Severe Impairment Battery. The data included precise details about the disease condition, study population, study design, results, significant observations and the limitations as well.

Materials and Methods

Umbrella Review Concept

We carried out an umbrella systematic review on the meta-analysis studies to identify the modifiable risk factors for AD. Rather than executing the systematic reviews from the beginning, the current umbrella review combines the available reviews and meta-analyses of the risk factors of AD and the potential therapies. We particularly selected cholinergic damage and inflammation as the two major factors promoting AD, and examined the effects of ChEIs and

Table I. Essential factors examined for meta-analysis.

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Kobayashi et al	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Xu et al	Y	Y	Y	Y	NA	Y	Y	N	Y	Y	N
Tariot et al	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N
Jansen et al	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y
Jiang et al	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y
Leinonen et al	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y
Matsunaga et al	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N
Miguel-Alvarez et al	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N
Gupta et al	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y
Szekely et al	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Tsoi et al	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Wang et al	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Abbreviations used: Y-Yes; N-No and NA-Not applicable Q1: Is the objective of the review and meta-analysis article precise and prominent? Q2: Was the article relevant in terms of the search? Q3: Was the study population well defined? Q4: Was the strategy of the study relevant and proper? Q5: Were the techniques appropriate? Q6: Were the data reliable? Q7: Was the study statistically significant? Q8: Were there too many limitations in the study? Q9: Did the study offer any new view on the concept? Q10: Was there any bias assessment? Q11: Were there any future directions for the study?

NSAIDs on the disease progression. The present umbrella review and meta-analyses followed the standardized methods and principles described before[39-41].

Inclusion criteria

Type of Participants

AD patients belonging to different age groups, stage and severity were selected for the umbrella review.

Kind of Exposure

The studies included patients exposed to the ChEIs, donepezil, galantamine and rivastigmine, and the NMDA receptor antagonist, MEM, or their combinations. Our umbrella review also comprised meta-analyses of the effects of NSAID exposure in AD patients.

Outcome Category

The preventive effects of ChEIs, MEM and NSAIDs in attenuating the symptoms of AD were the outcome measures. Adverse side-effects and drug-induced toxicities have also been noted.

Study Types

Systematic reviews and meta-analyses were generally included. Meta-analyses that were not part of organized reviews had been excluded from our study (Table I).

Search Strategy and Eligibility Criteria

A two-step search strategy was used to screen all pertinent studies and reviews on meta-analyses published in PUBMED. Studies published in English, and between January 2000 to August 2016 were included in our search. The titles and abstracts were first examined. From the screened articles, the references were checked and the cross-references were searched for additional meta-analyses studies and reviews. We scanned the key words, "Alzheimer's disease", "risk factors", "inflammation", "NSAID" and "acetylcholinesterase inhibitors". "Alzheimer's disease" was common along with all other search words (Figure 1).

Data Extraction and Synthesis

The data collected included minute details regarding the dietary factors, age, sex, education, study protocol, statistical analysis methods, results and implications. We considered studies that included health controls. The included reviews and meta-analyses provided the risk estimates of odds ratio (OR), risk ratio (RR), standardized mean difference (SMD), confidence intervals (CI) and population size. We checked for overlapping references and research studies within the systemic reviews and meta-analyses.

Results

Patient Health Factors-Risk Factors in AD

The systematic reviews and meta-analyses that had been examined considered the diet and ge-

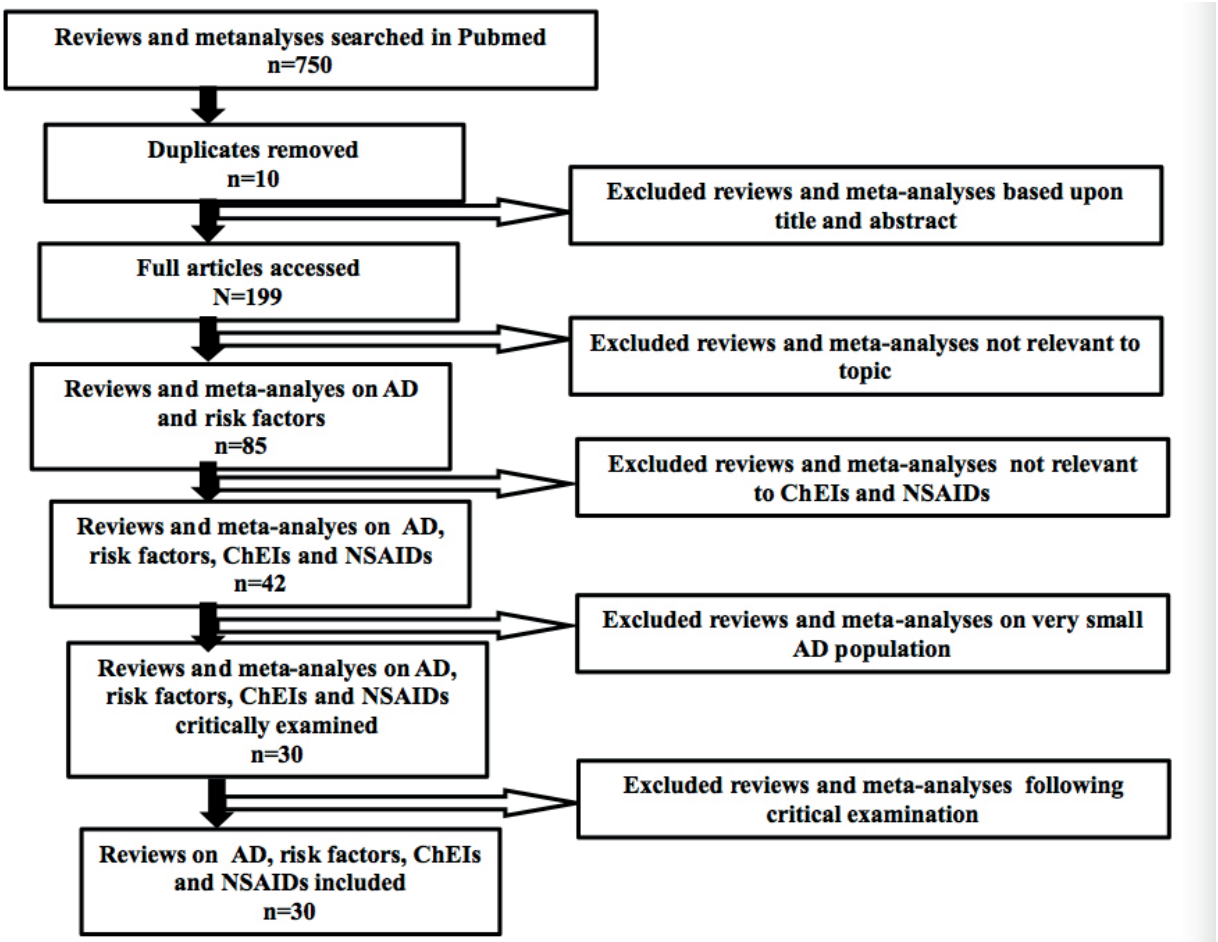

Figure 1. Flow chart of the strategy adopted for searching and selecting relevant reviews and meta-analyses on AD, risk factors, ChEIs and NSAIDs.

neral health status of AD patients. There were two sets of factors; firstly, diet, psychological condition and lifestyle, and secondly age, gender, literacy and education (Table II).

Diet, Psychological Condition and Lifestyle

Search studies had been conducted for potential cohort and retrospective case-control studies from Cochrane Database of Systematic Reviews and PUBMED[15]. The studies were particularly based upon the meta-analysis of "Observational Studies in Epidemiology Group" and the "PRISMA 2009 guidelines for systematic review and meta-analysis"[42-44]. The inclusion criteria comprised data on OR and RR of AD among a general population, and for the exposures that were known to affect AD[15]. The control population included the arbitrarily chosen healthy individuals with no history of cognitive failures. The individuals were devoid of cardiac problems[15]. The male and female participants were compared independently[15]. Additionally, as per the Newcastle-Ottawa scale, following proper OR/RR assessments, no exclusion criteria were incorporated in the study[15]. For obtaining a statistically significant data (95% probability) through the I2 statistic (Egger test and Stata V.12.0), a pooled data from several studies were obtained[15]. Firstly, the controls, and then the AD population underwent examination[15]. The risk factor analysis was performed, and the conclusions were drawn as grade-I, II-B and II, based upon the heterogeneities of >5000 (I2≥50%), <5000 (I2≥50%) and <5000 (indicating prominent heterogeneity), respectively[15,45]. With a relatively larger pooled population (>5000, grade I and II-A), seven factors, such as neuroticism, Aβ42/40 ratio, fish eating habits, dietary pattern, education status, physical activities and smoking habits in Asian

Table II. Meta-analyses of risk factors in AD.

Risk factors	Parameters tested	Population size	OR and RR	CI	Heterogeneity
Diet (Xu et al)	Fish eating habits and dietary pattern		Applied	95%	I2 statistic applied
Sex, (Xu et al; Jansen et al)	Both male and female				
Cancer history (Xu et al)	Both cancerous and non-cancerous population	>5000			
Osteoporosis (Xu et al)	Both osteoporotic and non-osteoporotic patients				
Family history (Xu et al)	Cancer and dementia				
Habits (Xu et al)	Smoking				
Education (Jansen et al)	Literacy and awareness	7583	NA	95%	I2 statistic applied (>50%)
Apo E genotype status (Jansen et al)	Apo E alleles				
Age (Jansen et al, Morris et al)	MCI, aging and amnesia	241	NA	95%	I2 statistic applied
CNS disorders (Jansen et al, Morris et al)	Cerebrovascular dysfunction and depression				

Abbreviations used: OR-Odds ratios (OR); RR-Relative risk or risk ratio; CI-Confidence intervals; ApoE-Apolipoprrotein E; MCI-Mild cognitive impairment.

populations (Table II) appeared as the key factors for meta-analysis[15]. Neurodegeneration, marked by impaired gait and behavioral aberrations, and cancer and malignancy served as major factors regulating AD development[15]. While degeneration and failed health conditions promoted the probabilities of AD, persons with cancer history had reduced possibilities, to the extent of about 37-40% attenuation in the likelihood of developing AD[15]. The importance of Ca^{2+} ion transpired from a meta-analysis study that demonstrated AD risk, with scores of RR=2.07 and CI value of 1.22-2.92 in osteoporotic patients[15]. Supporting this concept, exposure to sunshine and treatment with vitamin D attenuated the chances of developing AD[15].

Age, Gender, Literacy and Education

Individual data meta-analysis to understand the occurrence of cerebral amyloid pathology was conducted on participants having normal memory performances in comparison with those with mild and prominent cognitive impairments[46]. The risk factors examined were age, gender, literacy, education and the ApoE genotype status[46,47]. To identify statistical relevance, the meta-analyses were carried out on the total study population directly, and after combining data, the generalized estimating equations were examined, based on the frequency and OR[46,48]. The meta-analyses revealed that *APOE*-ε4 carriers and non-carriers, and age factor played a marked role in enhancing amyloid burden and cognitive dysfunction[46,49]. Notably, while the sex of individuals had no significant impact, education status bore a prominent link with the amyloid count[46]. Mild cognitive impairment (MCI) appeared as a risk factor, and differences were observed for patients with non-amnestic MCI and amnestic MCI, the latter demonstrating a greater amyloid burden[46,47]. However, although amnestic MCI showed strong association with AD pathology, certain other central nervous system disorders, such as cerebrovascular dysfunction, depression and hippocampal sclerosis, marked

by neuronal loss and gliosis also exhibited MCI features[46]. Comparative analysis of *APOE*-ε3 and the *APOE*-ε4 alleles revealed the latter to be more at risk for AD, being expressed at an early age as well[46,50]. Contrarily, *APOE*-ε2 allele appeared protective, and a comparatively higher *APOE*-ε4 level led to the clinical manifestations of AD[46,51]. Thus, all these factors served as inclusion criteria for our umbrella review of meta-analyses on AD targeted therapies.

Cholinesterase Inhibitors and Memantine as AD Therapies

ChEI+MEM Therapy

Meta-analysis using neuropsychiatric inventory (NPI) of three studies indicated that ChEI+-MEM in combination was a true therapy for moderate-to-severe forms of AD, with a high significance, $p=0.00001$[35]. To explore this aspect, a search through Review Manager that included seven pooled-up studies on randomized controlled trials (RCTs) for the combination treatments in 2182 patients was performed[35]. MEDLINE and Cochrane database, Google Scholar, Excerpta Medica database (EMBASE), CINAHL and PsycINFO citations were searched, and a range of drugs and ChEIs were scanned[35]. The outcomes assessed were cognition and neurobehavior, through Severe Impairment Battery (SIB), ADAS-cog, SMMSE, MMSE and NPI[52]. The statistical analysis, using the DerSimonian-Laird random-effects model, was based on mean standard deviation (MSD) data with 95% confidence intervals[53]. The NPI for behavioural assessment for combination therapy showed better results than placebo[54]. However, contradictions were observed in the NPI statistical data, and it could be inferred that meta-analyses and studies with higher sample numbers may be essential to conclude about use of ChEI+MEM as AD therapy.

A meta-analysis study revealed that AD drug treatment, whether early or late, had the same effects on cognition, behavioral aspects and other physical and physiological status[55]. Using the SMD of data obtained from meta-analysis, and pooling the data of about 1415 patients and for eight trials tested for cognition, revealed no significant difference between early and late treatments[55]. A meta-analysis study by another group that compared the effects of ChEIs and MEM with the placebo for an AD population, along with a follow-up period of 3 to 12 months showed a prominently better effect for the ChEI compared to MEM[56,57]. However, the adverse side-effects of MEM were relatively less than ChEI[31,55]. Nonetheless, the studies had some deficits. Critically assessing the studies, we inferred that the early and late time points had not been defined clearly, and the follow-up duration was not enough. The patients used for the meta-analyses showed very slow and little cognitive loss[55], and we assumed that there was a probable heterogeneity in the physical status of patients. Hence, to reach a perfect conclusion for early versus late treatment effects, we presume that more studies may be needed with larger patient size and an extended follow-up time following MEM or ChEI treatments (Table III).

Donepezil+MEM Therapy

For meta-analysis of ChEI and MEM, a pooled data revealed an MMSE range of 5-14 for some studies and 10-22 for few others[58-60]. However, all the groups preferred a combination therapy compared with individual. For the study by Tariot et al[58] with AD patients suffering from severe dementia, a statistical significant improvement appeared in the SIB score following combinatorial treatments[58]. Furthermore, for donepezil and MEM treatments in Moderate to Severe Alzheimer's Disease (DOMINO) trial, a significant difference between the combination therapy and individual donepezil treatment was hardly apparent[59]. The MMSE study for DOMINO showed a comparable effect for combination therapy and donepezil alone treatment[59]. A similar trend was also observed for the mild to moderate AD[61], particularly in the open-label trials[62]. In another meta-analysis that had been conducted for a long span of time, from 1997-2005, an identical pattern was observed[63]. We deduced from the pooled up data for studies on donepezil+MEM therapy that patient heterogeneity and more importantly an extended period of enrolment may have been the pertinent reasons behind the differential observations. The Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory (ADCS-ADL) analysis method, based on SMD calculation of the results from blinded-randomized clinical trials, significantly favored combination therapies for AD compared to MEM monotherapy in the DOMINO trial[58]. However, the data appeared quite dissimilar for donepezil[58], indicating a better effect of the drug alone. A variation was observed for the different ADCS-ADL studies. While AD-SC-ADL-19 version of measurement in moderate

Table III. Meta-analyses of ChEI and memantine therapy in AD.

Treatments	Search strategy	Scale	Statistics	Outcomes	Limitations
AChEI+memantine (Matsunga et al)	i. MEDLINE ii. Cochrane database iii. Google Scholar iv. EMBASE v. CINAHL vi. PsycINFO	i. SIB ii. ADAS-cog iii. SMMSE iv. MMSE v. NPI	95% CI and SMD values	Beneficial for moderate-to-severe AD	Contradictions in NPI statistical data
AChEI, donepezil, galantamine, rivastigmine or memantine (Tsoi et al)	i. MEDLINE, ii. EMBASE, iii. AMMED	i. Cognition ii. SIB iii. NPI iv. ADCS-ADL v. MMSE vi. Physical function	95% CI and SMD values	Early drug treatment based upon earlier diagnosis poses no advantage in attenuating AD manifestations for short term	i. Clinical heterogeneity ii.Treatment conducted iii. MMSE very high
Donepezil+ memantine Tariot et al)	Not mentioned	i. SIB ii. MMSE iii. CIBIC-Plus	SD value	Detected inaccuracies in previous meta-analyses studies	i. Claimed inclusion of patients of heterogeneous categories ii. Comparisons were not appropriate
Comparative efficacies of ChEIs (Kobayashi et al)	i. PubMed ii. EMBASE iii. Cochrane dementia	i. ADAS-Cog ii. NPI iii. CIBIC iv. CGIC	95% CrI	i. Demonstrated modest beneficial role of ChEIs ii. Detected beneficial effects for donepezil and rivastigmine, but not for galantamine	i. Variability in study size ii. The number of trials were very small iii. Used flexible drug doses iv. Drug tolerability less examined
ChEIs and atypical antipsychotics (Wang et al)	i. PubMed, ii. EMBASE, iii. Cochrane Controlled Trials iv. Cochrane Database of Systematic Reviews	NPI and safety outcome ITT analysis MMSE	95% CI SMD	ChEIs and atypical antipsychotics could improve neuropsychiatric symptoms in AD patients, but with bad safety outcomes.	i. NPI appeared comprehensive ii. Use of other drugs consumed was unrecorded iii. Trial number few for antipsychotics, antidepressants and mood stabilisers iv. Patients had physiological variability while pooling data

Abbreviations used: EMBASE-Excerpta Medica database; CINAHL-Current nursing and allied health Literature; AMMED-Army medical department; SIB-Self-injurious behavior; ADAS-cog-Alzheimer's disease assessment scale-cognitive; SMMSE: Standardized mini-mental state examination; MMSE-Mini mental state exam; CIBIC-Plus: Clinician's interview-based impression of change Plus caregiver input; NPI: Narcisistic personality inventory (NPI); ADCS-ADL: Alzheimer's disease cooperative studies activities of daily living inventory; ITT: Intention-to-treat; CGIC: Clinical global impression of change; CI-Confidence intervals; CrI-Credible interval; SMD- Standardized mean difference

to severe dementia showed improvements with donepezil treatments, ADCS-ADL-23 failed to do so[60]. Diverse observations were also obtained for primary and secondary outcome measu-

res. In Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC)-Plus method, results showed prominent improvements with the donepezil therapies for mild to moderate patients in case of primary outcome measure[58], whereas the findings were entirely different for secondary outcome measure, showing no improvements at all[60]. The CIBIC-Plus method of measurement also proved to be less consistent and quite insensitive[64,65]. NPI analysis as a secondary outcome measure also favored combination therapy[58], especially when compared with MEM monotherapy[59]. Nonetheless, we found that these studies had some limitations in assessment of learning-memory and functional outcomes. We observed that a certain degree of variability entered in the statistical analysis, and a few data had been calculated based on standard errors (SEs) and some on standard deviation (SD), and the quantification for SMD was also on dissimilar versions of scales[59]. There were some variations in the patient conditions as well, where some had been suffering from severe forms of AD while others quite milder[59]. Minimal clinically important difference score (MCID) appears to be another meta-analysis score that well correlates the results with the chances at the clinical levels[66]. Of RCTs, the study elaborated by Howard et al[59] was the only one that considered MCID score, while for the others, such as Tariot et al[58] and Posteinsson et al[60], results were based upon CIBIC-Plus score merely[67]. A prominently big patient sample size and a minimum of one year proved essential for the MCID score[67] (Table III).

Comparative Effects of Donepezil, Galantamine and Rivastigmine

Using AD and ChEIs as key words in PUBMED and EMBASE, a recent systematic meta-analysis and Bayesian network meta-analysis (NMA) of donepezil, galantamine and rivastigmine were carried out to understand their comparative efficacy and safety in mild to moderate AD[68]. A total of 19 studies were performed on these three drugs with AD patients from North America and Europe. The average age of the patients was around 69 to 78, with about 62% being women[68]. The MMSE score varied between 15-21, and the ADAS-Cog and NPI were between 20-35 and 10-35 respectively[68]. The cognitive effects were primarily taken into consideration[68]. Inclusion and exclusion criteria and data extraction were based on RCTs, and the scores included ADAS-Cog, NPI, CIBIC-plus and Clinical Global Impression of Change[69]. A comparative effect of drugs was examined[68]. Severe AD patients, with an MMSE value <10, and patients treated at either very high or minimum doses of the ChEI inhibitors were not included in the study[68]. The data extraction process was performed and cross-checked by more than two people[68]. At first, heterogeneities were assessed using the conventional meta-analysis procedure of I2 statistic and funnel plots, followed by Metafor package[68]. The comparative NMA was conducted for two doses of donepezil (5 and 10 mg), galantamine (16 and 24 mg) and rivastigmine (6 and 12 mg)[68]. Following this, the assessments were performed through the Bayesian hierarchical model using Markov chain Monte Carlo estimation and the GeMTC network meta-analysis package as a support[70]. The study revealed that ChEIs improved cognitive performances, but failed to cause improvements in neuropsychiatric symptoms, as evident from the funnel plot that hardly showed any change in distribution pattern[68]. Secondly, donepezil and rivastigmine appeared effective in the clinical global change data evaluated by the CIBIC+Clinicians' global impression of change (CGIC), whereas galantamine failed to show any remarkable improvement relative to the placebo[68]. However, cognitive tests demonstrated galantamine dose of 24 mg to be helpful[68]. The I2 values had a heterogeneity score of 44-53% and CGIC showed I2 heterogeneity between 64-51% respectively[68]. Tolerability assessments for nausea, dizziness, drowsiness, vomiting, diarrhea and dysentery, and withdrawal effects were the minimum for donepezil and maximum for rivastigmine[68]. Thus, supporting an earlier study, donepezil seemed to be the safest ChEI for AD treatment[71].

Another study methodically searched for AD, ChEI treatments and the disease manifestations through PubMed, EMBASE, Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register[72]. In addition to cognitive and neuropsychiatric symptoms, the scan also included dementia and general behaviour[72]. Other than the typical ChIEs, the effects of a wide-range of other closely associated drugs, such as anti-depressants, anti-convulsants, sedatives and psychotropic drugs were searched[72]. Double-blinded, RCTs against placebo controls were included in the study[72]. Both crossover and non-crossover trials had been carried out, and the patients were all prone to AD[72]. The assessment ranges of doses for these drugs were wide, and the NPI was found to range between 10 to 12[72]. The sample size,

age, gender, race, treatment schedule and side-effects were assembled[72], and the total search was performed by three reviewers[72]. The statistical analysis generated SMD data of NPI-10, NPI-12 and NPI- with 0.05% *p*-values[72]. The RR analysis was accomplished and heterogeneity was examined visually and by a combination of chi-squared test (χ^2) and I2 tests[72]. The data analysis and statistical software, STATA12.0, was used and Bias detection funnel plots and Begg's test method were adopted[72]. A total of 32 studies were analyzed that included RCTs and placebo-controlled trials[72]. Sixteen trials were on a single dose of drugs, and the others on dose range of the drugs[72]. The number of treated patients in trials was close to 7000 and placebo was around 5000[72]. The drugs included ChEIs, anti-depressants, anti-psychotics, mood-elevators, MEM, etc. The patients belonged to the age group of 74-86, and the MMSE was between values of 4.5 to 21, and the patient population was from Europe and North America[72]. Fifteen studies that included donepezil (eight trials), galantamine (four trials) and metrifonate (three trials), and the fifteen RCTs for ChEI treatment showed significant ($p<0.05$) behavioral improvements for all drugs[72]. The meta-analysis study revealed marked improvement in NPI score, with a standardized mean difference of 0.12 and CI of 0.25[72]. A substantial heterogeneity (I2) was observed[72], probably due to the difference in ages, medicine sub-types and brands, population heterogeneity, racial differences, MMSE, treatment period, etc. The sensitivity assessment for the studies that used intention-to-treat method revealed beneficial effects of ChEIs against placebo[73]. However, the effects were comparatively better for galantamine (SMD −0.13; 0.05%, CI −0.2 to −0.03 and I2=0%) in terms of improvements in neurobehavior and neuropsychiatric symptoms compared to donepezil ($p<0.0$, CI value between 0.2-0.10 and I2 around 7)[73]. The meta-analysis also revealed marked benefits with anti-psychotic drugs, quetiapine, olanzapine, aripiprazole, ziprasidone, olanzapine and clozapine, compared to placebo on the NPI score scale[72]. Bias risk assessment through Begg's test and the Funnel Plot demonstrated little publication bias (z=0.60)[72]. Comparing the impacts of the anti-psychotics proved that olanzapine was the most effective in improving neurobehavior and neuropsychiatric symptoms (SMD −0.20; *p*-value of 0.0%, CI −0.30 to −0.0 and I2 -0) followed by aripiprazole (SMD −0.20; *p*-value of 0.0%, CI −0.30 to −0.04; I2-1)[72]. RCT on 20-24 AD patients who belonged to one group and about 120-124 patients in the other using anti-depressants, such as sertraline, fluoxetine, citalopram and trazodone, was carried out[72]. However, the NPI score showed a non-significant difference between the placebo and treated patient population, indicating minimum beneficial effects of anti-depressants among the patients[72]. An RCT on 13-14 AD patients using a valproate mood stabilizer treatment for six weeks, followed by a two-week observation showed marked changes in the NPI scores[72]. Meta-analysis study for MEM for eight RCTs that involved around 1500 MEM-treated AD patients compared to 1333 placebo patients showed no significant effects in the NPI score, indicating the non-beneficial effects of MEM[72]. However, the heterogeneity existed (I2=70-80%), based upon variations in age, race, span of drug treatment (3-7 months), MMSE, etc.[72]. Assessing the neuropsychiatric changes through NPI or another new scale, the Behavioural Pathology in Alzheimer's Disease also revealed significant improvements by ChEIs and anti-psychotics (ChEIs, SMD −0.11; 95% CI −0.20 to −0.01; atypical antipsychotics, SMD -0.18; 95% CI −0.27 to −0.09). The impacts of MEM and anti-depressants were very little (MEM, 95% CI −0.27 to 0.01; antidepressants, 95% CI −0.35 to 0.37)[72] (Table III).

Treatment Impact of NSAID in AD

AD is a neuro-inflammatory disorder, and NSAIDs are used in attenuating the disease pathogenesis[19]. A meta-analysis search through PUBMED, Cochrane Database and biological abstracts using the words, AD, NSAID and inflammatory diseases was conducted[38]. The screening identified around 2000 abstract and 35 relevant and interesting studies[38]. The detail regarding the participants, such as, location, age, gender, family, etc., was taken into consideration[38]. Additionally, the disease onset-time and NSAID treatments were all thoroughly inspected[38]. The studies that included drug treatments for 2-3 years or life-long were included and the Stata 7.0 software package was used for the quantitative analysis. The I2 heterogeneity and statistical program, such as, Q-statistic, Egger's plots and Begg's funnel plots were used for the meta-analysis[38]. Of all the studies analyzed, about eleven of them appeared to have a tangible link between NSAID and AD risk. Of these, there were eight studies that demonstrated an apparent association between NSAID treatment and AD[74-76]. Both non-prospective (seven) and prospective (four) studies that

included OR and RR respectively was examined, and the results from the prospective groups that involved NSAID treatment as preventives appeared more conclusive[38]. Non-prospective studies, on the other hand, involved retrograde method of data assessment, and showed a chronological association between NSAID treatment and AD[38]. A certain degree of discrepancy appeared in the meta-analysis, where the prospective studies indicated a 25% and 60% lesser risk for AD for the 2-3 years and continued life-long treatments respectively[38]. The study also emphasized upon the fact that treatment with NSAIDs delayed the onset of AD[38]. Thus, it could be inferred from the meta-analysis that a prolong treatment with NSAIDs could be more effective compared to a shorter span. Analyzing the data from the Canadian Study of Health and Aging revealed a marked resemblance in the OR values for NSAID and its link with AD and the inflammatory disease, arthritis[76]. Meta-analyses were performed to clearly understand the usefulness of NSAIDS, ibuprofen, rofecoxib, celecoxib, aspirin, naproxen, nimesulide, tarenflurbil and indomethacin as therapeutics for AD[28]. The experimental population included AD patients undergoing NSAID treatment, and patients with three-month follow-up[28]. The search was carried out using the "Patient Population or Problem, Intervention treatment, Comparison, Outcomes, and Setting method", and the Cochrane Library electronic databases in combination with PUBMED[28]. The PRISMA guidelines were followed, where a total of 963 articles were reviewed[77]. Following initial screening for pertinent publications, the inclusion criteria were adopted, and Cochrane Collaboration tool was applied[28]. Age, APOEe4 allele carriers, dose, duration and frequency of NSAID treatments of the participating patients were the major factors taken into considerations[28]. The cognitive performances of patients were examined, and scores were determined and the outcome reported as ADAS-cog[28]. The ADAS-cog scale was found to be between 0-70, and a lower score indicated better performance[78]. The second measurement scale was "Clinical Dementia Rating Scale sum-of-boxes" that examined learning memory performances, rationality, difficulty in solving ability, social behaviour, domestic affairs and personal hobbies[28]. Another vital factor contemplated was whether the drug had any impact on the ability to cope with activities of daily living. It was found that each factor was between a scale of 0-3, and the total maximum score was 18, signifying worst performances[79]. The third scale used for memory impairment was MMSE, where the scale ranged from 0-30, and scores <10 suggested severe forms of AD[77]. Statistical examination of the studies was based on SD of the changeable variables and the size of samples assessed through Begg's test[80]. The measurements were carried out in MIX 2.0 Pro for Excel software, and a 95% *p*-value was considered significant[80]. Interestingly, despite a rigorous examination through enough patient sample size and relevant controls, the effect of NSAID through the meta-analysis study appeared less significant, with *p*-values > 0.05[28]. Analyzing the study, it could be inferred that a prior treatment with NSAID may probably have a better impact compared to its treatment following diagnosis[28]. Hence, it may also be presumed that because the study lacked subjects from preventive groups, the observations showed little therapeutic effects for the NSAIDs[28]. Secondly, the number of NSAIDs used in meta-analysis was small[28]. However, although the data appeared negative, this meta-analysis is one of the very few on NSAID and AD, and appears important as it emphasized the need for newer studies in this context[28]. Another meta-analysis that explored the relationship between NSAIDs and AD based on RCTs, PUBMED search, EMBASE and Cochrane Database Search Strategy also contradicted the therapeutic role of NSAIDs in AD[37]. The search included seven studies that comprised ADAS-cog and MMSE measures for clinical drug trails in AD[37]. The Neyeloff et al[81] method for statistical assessment of SMD with 95% probability factors was adopted[81]. The I2 statistic method of heterogeneity at a range of 0-40%, 30-60%, 50-90% and 70% to 100% showed non-heterogeneity, modest, considerable and extensive heterogeneity respectively[37]. Neither the ADAS-cog nor MMSE showed any changes in NSAID-treatments compared to the placebo and differed considerably from the observational findings[82]. Additionally, the search from this study revealed a match with the "Alzheimer's Disease Anti-inflammatory Prevention Trial study" that demonstrated the failure of NSAIDS, naproxen or celecoxib, to ameliorate cognitive impairments in an RCT study of USA[83]. Nonetheless, supporting the data obtained from the above study, it could be inferred that the RCT for long term (more than a year) NSAID exposure may be more important for meta-analysis[37]. Secondly, the amount of NSAID that reaches the brain, and whether that is sufficient for being effective

also needed investigation[37]. Because of these negative results from the meta-analysis studies on NSAIDs and clinical trials on AD, few studies have been conducted along this line. Hence, studies on a larger cohort of RCTs and cognition are needed. Moreover, it is viewed that rather than the conventional NSAIDs, studies may better be conducted with the selective Cyclo-oxygenase (COX)-2 inhibitors as treatments for AD[84]. Meta-analysis of RCTs with a mixture of NSAID and COX-2 inhibitors may as well be beneficial for the purpose[84] (Table IV).

Discussion

To our knowledge, this appears to be the first updated umbrella review of meta-analyses that examines a wide range, from risk factors to the most prevalent therapies in AD. We identified diet, psychological condition, lifestyle, age, gender, literacy, education and genotype status as major determinants of AD. The current review also supports that administration of ChEIs and MEM may attenuate AD progression. However, although observational studies claim NSAIDs to be playing a major therapeutic role in AD, our umbrella review fails to reinforce this existing concept.

This appears to be the first complete and precise systematic umbrella review and meta-analysis to date, which considers nearly all known variable risk factors for the neurodegenerative disorder, AD. Our work involves a detailed search of meta-analyses studies of risk factors that could be intervened by life-style changes, or through preventive, prophylactic, therapeutic and clinical measures. Our findings highlighted the heterogeneity of variable risk factors for AD and also pointed at the intricacies of the disease etiology.

Table IV. Meta-analyses of NSAID therapy in AD.

Treatments	Search strategy	Scale	Statistics	Outcomes	Limitations
NSAID: diclofenac, indomethacin naproxen, ibuprofen, tarenflurbil naproxen, ibuprofen or tarenflurbil (Miguel-Alvarez et al).	i. MEDLINE, ii. Science Direct iii. Cochrane Library	i. ADAS-cog. ii. CDR-SOB iii. MMSE	95% CI and standard deviation	Non-beneficial effect of NSAIDs for AD in efficacies	All NSAIDs were given equal consideration, despite differences
COX-inhibitors (Gupta et al)	i. MEDLINE, ii. EMBASE, iii. COCHRANE databases	i. MMSE ii. ADAS-cog	95% CI and standard deviation	As opposed to observational studies, effects in the meta-analysis study showed non-significant effects of NSAID in AD	i. Clinical heterogeneity ii. Treatment conducted for short term iii. MMSE very high
Non-aspirin NSAIDs Szekely et al)	i. Medline, ii. Biological abstracts, iii. Cochrane Library iv. DSM v. NINCDS-ADRDA	i. Cognitive score ii. Activities of daily living score iii. SIB iv. MMSE v. CIBIC-Plus	i. Stata 7.0 software package ii. Q statistic (Stata meta program) iii. Begg's funnel plots and Egger's plots iv. Stata metabias	Prospective and non-prospective tudies showed that NSAIDs reduced AD risk	i. Claimed inclusion on observational settings ii. History of patients less known iii. Inappropriate comparisons

Abbreviations used: NSAID: Non-steroidal anti-inflammatory drugs; EMBASE: Excerpta Medica database; SIB: Self-injurious behavior; ADAS-cog: Alzheimer's disease assessment scale-cognitive; SMMSE: Standardized mini-mental state examination; MMSE-Mini mental state exam; CIBIC-Plus: Clinician's interview-based impression of change Plus caregiver input; CI-Confidence intervals; CDR-SOB-Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB); NINCDS-ADRDA-National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; DSM-Diagnostic and Statistical Manual.

The analysis suggested that a careful consideration of the dietary patterns, education status, physical activities and smoking habits may prevent AD pathogenesis. The results indicate that potential interventions in behavioral conditions, mental and physical degeneration, pre-existing disorders, such as cancer, vascular dysfunctions, bone erosion, etc., may be promising selective strategies for preventing AD[15]. Additionally, age, low education level, and most importantly ApoE genotype status played vital determining role in AD[46,50], and thus deserve special attention. Based on our data, additional studies on AD risk factors, particularly the physiological conditions and risk genotypes of patients appear predominantly essential. Good-quality and large population-based investigations and RCTs are also needed to conclude upon the risk factors. Moreover, increased surveillance and awareness spread may as well be promising ways for preventing the disease progression, particularly for the less-educated and economically backward class.

A major conclusion of this umbrella review and meta-analysis is the evidence for the effectiveness and safety of ChEIs in AD patients. The current review analyzed the effects of ChEIs and memantine from several reports and found diverse effects. Meta-analysis study by Kobayashi et al[68] detected that ChEI treatment significantly improved cognitive performances in AD[68]. However, the effects on neuropsychiatric symptoms appeared inconclusive. The Bayesian NMA data offered a comparative participation of donepezil, galantamine and rivastigmine in attenuating AD symptoms, and eventually proved greater therapeutic efficacies of donepezil and galantamine relative to rivastigmine[68]. We found the paper by Kobayashi et al[68] to be a rare and essential one in terms of ChEI and AD. However, we observed that few groups suggested ChEI+MEM as a better therapeutic strategy compared to ChEI monotherapy[35,55]. Matsunaga et al[35] reported that ChEI+MEM combination therapy was more effective for moderate-to-severe AD[35]. Comparing the studies, we inferred that therapeutic strategies in AD are essentially dependent on the heterogeneity of stage and severity of AD. However, even for moderate-to-severe AD, the combination of galantamine and MEM failed to show any prominent impact[35]. This discrepancy could be explained by the differences in their functioning. While galantamine alters the functioning of nicotinic receptors[85], MEM has the potential to block the same receptors[86]. These two contradictory features may have nullified the effects of each other, resulting in a net non-effectiveness in improving cognitive performances in AD patients. Interestingly, the results of Tsoi et al[55] showed that patients exposed to early diagnosis and early treatment with the ChEIs and MEM had a small beneficial effect on the cognitive performances in AD patients[55]. Thus it may be deduced that, although early recognition of dementia and AD symptoms may perhaps have psychosocial advantages, an early therapeutic intervention may not be very beneficial. Thus, future investigations on extended follow-up observations may clear the doubts on early and late treatments with targeted drugs and the repercussions in AD patients. Another meta-analysis study proved that ChEIs not only improved the cognitive abilities, but also played a beneficial role in attenuating the neuropsychiatric problems[72]. The effects were less prominent for anti-depressants and MEM[72], suggesting the superior role of ChEIs in ameliorating cognitive deficits and neuropathology in AD. Neuropsychiatric aberrations comprise a vital manifestation in AD[87,88]. Prior to Wang's group, very few studies related the ChEIs with neuropsychiatric abnormalities, and thus through our umbrella review, we claim the need for future research on neuropsychiatric outcomes and ChEIs in AD.

Neuroinflammation is a well-known risk factor for AD[19]. Aβ and p-tau proteins stimulate astroglial and microglial activations that induce neuronal apoptosis, and thereby cognitive failures in AD[19]. Additionally, inflammation also promotes the generation of Aβ and p-tau, leading to a cycle of neurodegenerative events[19]. Thus, the current review that has brought together observations from the meta-analysis studies on NSAID and AD seems very useful and appropriate. Our work also underscores the contradictory findings of NSAIDs, and rationalizes the discrepancies. Preliminary evidence from the research of Miguel-Alvarez et al[28] failed to find any prominent improvements in cognition and severity of the disease manifestation when treated with NSAIDs[28]. However, these findings had a medical interest because other than the cognitive abilities, factors, such as social behaviour, attentiveness, language proficiency, and the ability to carry along with the daily activity had been examined as well[28]. Based upon the compiled data from ADAS-cog and MMSE scores, observations of Gupta et al[37] were almost

similar to that of Miguel-Alvarez et al[28]. The results hardly showed any difference between the NSAID-treated and untreated groups[28,37]. The results from the two meta-analysis studies were close to that observed in Alzheimer's Disease Anti-Inflammatory Prevention Trial study that showed a non-significant effect of naproxen and celecoxib in AD[89]. On the contrary, prospective and non-prospective studies by Szekely et al[38] strongly indicate that NSAIDs have a protective function in ameliorating AD and also preventing the disease occurrence[38]. However, a sustained treatment with NSAIDs was essential to attenuate the risk of AD[38]. Examining the study, we could infer that a long-term NSAID exposure is essential for treating AD. The previous meta-analysis studies that failed to link AD and NSAIDs may have fallen short in terms of treatment duration.

Limitations and Future Research

Although the meta-analysis studies and reviews accessed provided an idea on risk factors of AD and its therapies, particularly ChEIs, memantine and NSAIDs, the studies had several limitations. The primary drawback was the heterogeneity in the sample size, population, duration and physiological condition. Most of the studies involved patients of varied severities and low number of trials. The number of epidemiological and clinical studies were also few. Hence, higher number of human researches with careful consideration of study population traits, exposure assessment, age, gender specification, etc. is essential to draw a perfect conclusion from meta-analyses. Statistical analysis needs more precision, with distinct SE, SD and SMD data. Moreover, the findings for meta-analysis were obtained from published articles only, and hence a publication bias also appeared in the studies. For studies that recruited patient population through advertisements involved self-selection bias.

Hence, more detailed meta-analyses and superior-quality cohort studies are needed on risk factors, therapies and AD that report age, related drug treatments, neuropsychiatric symptoms, treatment span, etc. The definition of type and intensity of cognitive loss deserves special consideration. The cerebrovascular status that also determines the extent of AD pathogenesis [90] demands investigation. Most importantly, for all meta-analysis studies, RCTs with larger sample size and population and for longer follow-up periods are essential.

Conclusions

This systematic umbrella review and meta-analysis has identified and compiled relevant meta-analysis studies and reviews on risk factors of AD and therapies, particularly, ChEIs, MEM and NSAIDs. Our paper offers a profoundly helpful resource and reference for researchers and clinicians in the field of Alzheimer's neurodegeneration and therapies. Our umbrella review provides a pooled meta-analysis data on the advantages and disadvantages of ChEIs, MEM and NSAIDs as effective treatments for AD. Nonetheless, further research is essential to deduce a strong and robust recommendation for the use of these therapies in attenuating symptoms of the dreaded neurodegenerative disease.

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Conflicts of interest

The authors declare no conflicts of interest.

References

1) Tarawneh R, Holtzman DM. The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. Cold Spring Harb Perspect Med 2012; 2: a006148.
2) Schierle GS, Michel CH, Gasparini L. Advanced imaging of tau pathology in Alzheimer disease: new perspectives from super resolution microscopy and label-free nanoscopy. Microsc Res Tech 2016; 79: 677-683.
3) Koller D, Bynum JP. Dementia in the USA: state variation in prevalence. J Public Health (Oxf) 2015; 37: 597-604.
4) Naganuma T, Takemoto Y, Shoji T, Shima H, Ishimura E, Okamura M, Nakatani T. Cerebral white matter hyperintensity predicts cardiovascular events in haemodialysis patients. Nephrology (Carlton) 2013; 18: 676-681.
5) Asada T. [Prevalence of dementia in Japan: past, present and future]. Rinsho Shinkeigaku 2012; 52: 962-964.
6) Singhal BS, Khadilkar SV. Neurology in the developing world. Handb Clin Neurol 2014; 121: 1773-1782.
7) Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011; 1: a006189.

8) Stancu IC, Ris L, Vasconcelos B, Marinangeli C, Goeminne L, Laporte V, Haylani LE, Couturier J, Schakman O, Gailly P, Pierrot N, Kienlen-Campard P, Octave JN, Dewachter I. Tauopathy contributes to synaptic and cognitive deficits in a murine model for Alzheimer's disease. FASEB J 2014; 28: 2620-2631.

9) Hollands C, Bartolotti N, Lazarov O. Alzheimer's disease and hippocampal adult neurogenesis; exploring shared mechanisms. Front Neurosci 2016; 10: 178.

10) Raskin J, Cummings J, Hardy J, Schuh K, Dean RA. Neurobiology of Alzheimer's disease: integrated molecular, physiological, anatomical, biomarker, and cognitive dimensions. Curr Alzheimer Res 2015; 12: 712-722.

11) Scarabino D, Gambina G, Broggio E, Pelliccia F, Corbo RM. Influence of family history of dementia in the development and progression of late-onset Alzheimer's disease. Am J Med Genet B Neuropsychiatr Genet 2016; 171B: 250-256.

12) Lardenoije R, Iatrou A, Kenis G, Kompotis K, Steinbusch HW, Mastroeni D, Coleman P, Lemere CA, Hof PR, van den Hove DL, Rutten BP. The epigenetics of aging and neurodegeneration. Prog Neurobiol 2015; 131: 21-64.

13) Hullinger R, Puglielli L. Molecular and cellular aspects of age-related cognitive decline and Alzheimer's disease. Behav Brain Res 2016; may 16.

14) Ryan NS, Rossor MN. Correlating familial Alzheimer's disease gene mutations with clinical phenotype. Biomark Med 2010; 4: 99-112.

15) Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Zhao QF, Li JQ, Wang J, Yu JT. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry 2015; 86: 1299-1306.

16) Lyall DM, Ward J, Ritchie SJ, Gail D, Cullen B, Celis C, Bailey ME, Anderson J, Evans J, McKay DF, McIntosh AM, Sattar N, Smith DJ, Deary IJ, Pell JP. Alzheimer disease genetic risk factor APOE e4 and cognitive abilities in 111,739 UK Biobank participants. Age Ageing 2016; 45: 511-517.

17) Shi J, Lepore N, Gutman BA, Thompson PM, Baxter LC, Caselli RJ, Wang Y. Alzheimer's disease neuroimaging I. Genetic influence of apolipoprotein E4 genotype on hippocampal morphometry: An N = 725 surface-based Alzheimer's disease neuroimaging initiative study. Hum Brain Mapp 2014; 35: 3903-3918.

18) Wang YQ, Qu DH, Wang K. Therapeutic approaches to Alzheimer's disease through stimulating of non-amyloidogenic processing of amyloid precursor protein. Eur Rev Med Pharmacol Sci 2016; 20: 2389-2403.

19) Rogers JT, Lahiri DK. Metal and inflammatory targets for Alzheimer's disease. Curr Drug Targets 2004; 5: 535-551.

20) Foster TC, Kyritsopoulos C, Kumar A. Central role for NMDA receptors in redox mediated impairment of synaptic function during aging and Alzheimer's disease. Behav Brain Res 2016; S0166-4328: 30278-30279

21) Owen RT. Memantine and donepezil: a fixed drug combination for the treatment of moderate to severe Alzheimer's dementia. Drugs Today (Barc) 2016; 52: 239-248.

22) Auriel E, Regev K, Korczyn AD. Nonsteroidal anti-inflammatory drugs exposure and the central nervous system. Handb Clin Neurol 2014; 119: 577-584.

23) Anand P, Singh B. A review on cholinesterase inhibitors for Alzheimer's disease. Arch Pharm Res 2013; 36: 375-399.

24) Singh S, Kushwah AS, Singh R, Farswan M, Kaur R. Current therapeutic strategy in Alzheimer's disease. Eur Rev Med Pharmacol Sci 2012; 16: 1651-1664.

25) Noshita T, Murayama N, Nakamura S. Effect of nicotine on neuronal dysfunction induced by intracerebroventricular infusion of amyloid-beta peptide in rats. Eur Rev Med Pharmacol Sci 2015; 19: 334-343.

26) Cheng XL, Li MK. Effect of topiramate on apoptosis-related protein expression of hippocampus in model rats with Alzheimers disease. Eur Rev Med Pharmacol Sci 2014; 18: 761-768.

27) Guo CN, Sun L, Liu GL, Zhao SJ, Liu WW, Zhao YB. Protective effect of nicotine on the cultured rat basal forebrain neurons damaged by beta-Amyloid (Abeta)25-35 protein cytotoxicity. Eur Rev Med Pharmacol Sci 2015; 19: 2964-2972.

28) Miguel-Alvarez M, Santos-Lozano A, Sanchis-Gomar F, Fiuza-Luces C, Pareja-Galeano H, Garatachea N, Lucia A. Non-steroidal anti-inflammatory drugs as a treatment for Alzheimer's disease: a systematic review and meta-analysis of treatment effect. Drugs Aging 2015; 32: 139-147.

29) Wang J, Tan L, Wang HF, Tan CC, Meng XF, Wang C, Tang SW, Yu JT. Anti-inflammatory drugs and risk of Alzheimer's disease: an updated systematic review and meta-analysis. J Alzheimers Dis 2015; 44: 385-396.

30) Inestrosa NC, Sagal JP, Colombres M. Acetylcholinesterase interaction with Alzheimer amyloid beta. Subcell Biochem 2005; 38: 299-317.

31) Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, Zhu XC, Tan L. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 2014; 41: 615-631.

32) Galimberti D, Scarpini E. Old and new acetylcholinesterase inhibitors for Alzheimer's Disease. Expert Opin Investig Drugs 2016; 25: 1181-1187.

33) Plosker GL. Memantine extended release (28 mg once daily): a review of its use in Alzheimer's disease. Drugs 2015; 75: 887-897.

34) Thompson S, Lanctot KL, Herrmann N. The benefits and risks associated with cholinesterase inhibitor

therapy in Alzheimer's disease. Expert Opin Drug Saf 2004; 3: 425-440.

35) Matsunaga S, Kishi T, Iwata N. Combination therapy with cholinesterase inhibitors and memantine for Alzheimer's disease: a systematic review and meta-analysis. Int J Neuropsychopharmacol 2014; 28: 18 pii: pyu115.

36) Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984; 141: 1356-1364.

37) Gupta PP, Pandey RD, Jha D, Shrivastav V, Kumar S. Role of traditional nonsteroidal anti-inflammatory drugs in Alzheimer's disease: a meta-analysis of randomized clinical trials. Am J Alzheimers Dis Other Demen 2015; 30: 178-182.

38) Szekely CA, Thorne JE, Zandi PP, Ek M, Messias E, Breitner JC, Goodman SN. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. Neuroepidemiology 2004; 23: 159-169.

39) Catalan-Matamoros D, Gomez-Conesa A, Stubbs B, Vancampfort D. Exercise improves depressive symptoms in older adults: an umbrella review of systematic reviews and meta-analyses. Psychiatry Res 2016; 244: 202-209.

40) Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Parkinsonism Relat Disord 2016; 23: 1-9.

41) Campbell JM, Stephenson MD, Bateman E, Peters MD, Keefe DM, Bowen JM. Irinotecan-induced toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. Pharmacogenomics J 2016; doi: 10.1038/tpj.2016.58. [Epub ahead of print]

42) Green S, McDonald S. Cochrane Collaboration: more than systematic reviews? Intern Med J 2005; 35: 3-4.

43) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-2012.

44) Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-341.

45) Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011; 10: 819-828.

46) Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, Visser PJ, Amyloid Biomarker Study G, Aalten P, Aarsland D, Alcolea D, Alexander M, Almdahl IS, Arnold SE, Baldeiras I, Barthel H, van Berckel BN, Bibeau K, Blennow K, Brooks DJ, van Buchem MA, Camus V, Cavedo E, Chen K, Chetelat G, Cohen AD, Drzezga A, Engelborghs S, Fagan AM, Fladby T, Fleisher AS, van der Flier WM, Ford L, Forster S, Fortea J, Foskett N, Frederiksen KS, Freund-Levi Y, Frisoni GB, Froelich L, Gabryelewicz T, Gill KD, Gkatzima O, Gomez-Tortosa E, Gordon MF, Grimmer T, Hampel H, Hausner L, Hellwig S, Herukka SK, Hildebrandt H, Ishihara L, Ivanoiu A, Jagust WJ, Johannsen P, Kandimalla R, Kapaki E, Klimkowicz-Mrowiec A, Klunk WE, Kohler S, Koglin N, Kornhuber J, Kramberger MG, Van Laere K, Landau SM, Lee DY, de Leon M, Lisetti V, Lleo A, Madsen K, Maier W, Marcusson J, Mattsson N, de Mendonca A, Meulenbroek O, Meyer PT, Mintun MA, Mok V, Molinuevo JL, Mollergard HM, Morris JC, Mroczko B, Van der Mussele S, Na DL, Newberg A, Nordberg A, Nordlund A, Novak GP, Paraskevas GP, Parnetti L, Perera G, Peters O, Popp J, Prabhakar S, Rabinovici GD, Ramakers IH, Rami L, Resende de Oliveira C, Rinne JO, Rodrigue KM, Rodriguez-Rodriguez E, Roe CM, Rot U, Rowe CC, Ruther E, Sabri O, Sanchez-Juan P, Santana I, Sarazin M, Schroder J, Schutte C, Seo SW, Soetewey F, Soininen H, Spiru L, Struyfs H, Teunissen CE, Tsolaki M, Vandenberghe R, Verbeek MM, Villemagne VL, Vos SJ, van Waalwijk van Doorn LJ, Waldemar G, Wallin A, Wallin AK, Wiltfang J, Wolk DA, Zboch M, Zetterberg H. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015; 313: 1924-1938.

47) Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC. Mild cognitive impairment-beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004; 256: 240-246.

48) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003; 327: 557-560.

49) Jack CR, Jr., Wiste HJ, Weigand SD, Knopman DS, Vemuri P, Mielke MM, Lowe V, Senjem ML, Gunter JL, Machulda MM, Gregg BE, Pankratz VS, Rocca WA, Petersen RC. Age, sex, and APOE epsilon4 effects on memory, brain structure, and beta-amyloid across the adult life span. JAMA Neurol 2015; 72: 511-519.

50) [Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol 2010; 67: 122-131.

51) Suri S, Heise V, Trachtenberg AJ, Mackay CE. The forgotten APOE allele: a review of the evidence and suggested mechanisms for the protective effect of APOE varepsilon2. Neurosci Biobehav Rev 2013; 37: 2878-2886.

52) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.

53) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

54) Riverol M, Slachevsky A, Lopez OL. Efficacy and tolerability of a combination treatment of memantine and donepezil for Alzheimer's disease: a literature review evidence. Eur Neurol J 2011; 3: 15-19.

55) Tsoi KK, Hirai HW, Chan JY, Kwok TC. Time to treatment initiation in people with Alzheimer disease: a meta-analysis of randomized controlled trials. J Am Med Dir Assoc 2016; 17: 24-30.

56) Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013; 159: 601-612.

57) Lin JS, O'Connor E, Rossom RC, Perdue LA, Burda BU, Thompson M, Eckstrom E. In: editors. Screening for cognitive impairment in older adults: an evidence update for the U.S. Preventive Services Task Force. Rockville (MD): Agency for healthcare research and quality (US); 2013; Report No.: 14-05198-EF-1.

58) Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I, Memantine Study G. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004; 291: 317-324.

59) Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, Burns A, Dening T, Findlay D, Holmes C, Hughes A, Jacoby R, Jones R, Jones R, McKeith I, Macharouthu A, O'Brien J, Passmore P, Sheehan B, Juszczak E, Katona C, Hills R, Knapp M, Ballard C, Brown R, Banerjee S, Onions C, Griffin M, Adams J, Gray R, Johnson T, Bentham P, Phillips P. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012; 366: 893-903.

60) Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT, Memantine MEMMDSG. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res 2008; 5: 83-89.

61) Schneider LS, Insel PS, Weiner MW, Alzheimer's Disease Neuroimaging I. Treatment with cholinesterase inhibitors and memantine of patients in the Alzheimer's Disease Neuroimaging Initiative. Arch Neurol 2011; 68: 58-66.

62) Riepe MW, Adler G, Ibach B, Weinkauf B, Tracik F, Gunay I. Domain-specific improvement of cognition on memantine in patients with Alzheimer's disease treated with rivastigmine. Dement Geriatr Cogn Disord 2007; 23: 301-306.

63) Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer disease. Alzheimer Dis Assoc Disord 2008; 22: 209-221.

64) Quinn J, Moore M, Benson DF, Clark CM, Doody R, Jagust W, Knopman D, Kaye JA. A videotaped CIBIC for dementia patients: validity and reliability in a simulated clinical trial. Neurology 2002; 58: 433-437.

65) Joffres C, Bucks RS, Haworth J, Wilcock GK, Rockwood K. Patterns of clinically detectable treatment effects with galantamine: a qualitative analysis. Dement Geriatr Cogn Disord 2003; 15: 26-33.

66) Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989; 10: 407-415.

67) Burback D, Molnar FJ, St John P, Man-Son-Hing M. Key methodological features of randomized controlled trials of Alzheimer's disease therapy. Minimal clinically important difference, sample size and trial duration. Dement Geriatr Cogn Disord 1999; 10: 534-540.

68) Kobayashi H, Ohnishi T, Nakagawa R, Yoshizawa K. The comparative efficacy and safety of cholinesterase inhibitors in patients with mild-to-moderate Alzheimer's disease: a Bayesian network meta-analysis. Int J Geriatr Psychiatry 2016; 31: 892-904.

69) Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B, Schmitt FA, Grundman M, Thomas RG, Ferris SH. Validity and reliability of the Alzheimer's disease cooperative study-clinical global impression of change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11 Suppl 2: S22-32.

70) van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res Synth Methods 2012; 3: 285-299.

71) Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging 2008; 3: 211-225.

72) Wang J, Yu JT, Wang HF, Meng XF, Wang C, Tan CC, Tan L. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2015; 86: 101-109.

73) Lyketsos CG, Reichman WE, Kershaw P, Zhu Y. Long-term outcomes of galantamine treatment in patients with Alzheimer disease. Am J Geriatr Psychiatry 2004; 12: 473-482.

74) Landi F, Cesari M, Onder G, Russo A, Torre S, Bernabei R. Non-steroidal anti-inflammatory drug (NSAID) use and Alzheimer disease in community-dwelling elderly patients. Am J Geriatr Psychiatry 2003; 11: 179-185.

75) Zandi PP, Anthony JC, Hayden KM, Mehta K, Mayer L, Breitner JC, Cache County Study I. Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. Neurology 2002; 59: 880-886.

76) Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I. Risk factors for Alzheimer's disease: a prospective analysis from the canadian study of health and aging. Am J Epidemiol 2002; 156: 445-453.

77) Hamrick I, Hafiz R, Cummings DM. Use of days of the week in a modified mini-mental state exam (M-MMSE) for detecting geriatric cognitive impairment. J Am Board Fam Med 2013; 26: 429-435.

78) Kolibas E, Korinkova V, Novotny V, Vajdickova K, Hunakova D. ADAS-cog (Alzheimer's disease assessment scale-cognitive subscale)-validation of the slovak version. Bratisl Lek Listy 2000; 101: 598-602.

79) Tschanz JT, Corcoran CD, Schwartz S, Treiber K, Green RC, Norton MC, Mielke MM, Piercy K, Steinberg M, Rabins PV, Leoutsakos JM, Welsh-Bohmer KA, Breitner JC, Lyketsos CG. Progression of cognitive, functional, and neuropsychiatric symptom domains in a population cohort with Alzheimer dementia: the cache county dementia progression study. Am J Geriatr Psychiatry 2011; 19: 532-542.

80) Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KG. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. BMC Med Res Methodol 2006; 6: 50.

81) Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and Forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. BMC Res Notes 2012; 5: 52.

82) Etminan M, Gill S, Samii A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. Br Med J 2003; 327: 128.

83) Group AR, Martin BK, Szekely C, Brandt J, Piantadosi S, Breitner JC, Craft S, Evans D, Green R, Mullan M. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. Arch Neurol 2008; 65: 896-905.

84) Cakala M, Strosznajder JB. [The role of cyclooxygenases in neurotoxicity of amyloid beta peptides in Alzheimer's disease]. Neurol Neurochir Pol 2010; 44: 65-79.

85) Williams DK, Wang J, Papke RL. Positive allosteric modulators as an approach to nicotinic acetylcholine receptor-targeted therapeutics: advantages and limitations. Biochem Pharmacol 2011; 82: 915-930.

86) Pandya A, Yakel JL. Allosteric modulators of the alpha4beta2 subtype of neuronal nicotinic acetylcholine receptors. Biochem Pharmacol 2011; 82: 952-958.

87) Chung JK, Nakajima S, Plitman E, Iwata Y, Uy D, Gerretsen P, Caravaggio F, Chakravarty MM, Graff-Guerrero A. Beta-Amyloid Burden is not associated with cognitive impairment in schizophrenia: a systematic review. Am J Geriatr Psychiatry 2016; 24: 923-939.

88) McClam TD, Marano CM, Rosenberg PB, Lyketsos CG. Interventions for neuropsychiatric symptoms in neurocognitive impairment due to Alzheimer's disease: a review of the literature. Harv Rev Psychiatry 2015; 23: 377-393.

89) Group A-FR. Follow-up evaluation of cognitive function in the randomized Alzheimer's disease anti-inflammatory prevention trial and its follow-up study. Alzheimers Dement 2015; 11: 216-225 e211.

90) Ashok A, Rai NK, Raza W, Pandey R, Bandyopadhyay S. Chronic cerebral hypoperfusion-induced impairment of Abeta clearance requires HB-EGF-dependent sequential activation of HIF1alpha and MMP9. Neurobiol Dis 2016; 95: 179-193.