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Systematic review of atorvastatin for the treatment of Alzheimer's disease★

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Abstract

OBJECTIVE: To assess the clinical efficacy and safety of atorvastatin in the treatment of Alzheimer's disease.

DATA SOURCES: Medline (1948/2011-04), Embase (1966/2011-04), Cochrane Library (Issue 3, 2011), Chinese National Knowledge Infrastructure (1989/2011-04), and the Chinese Biomedical Literature Database (1979/2011-04) were searched for randomized clinical trials regardless of language. Abstracts of conference papers were manually searched. Furthermore, Current Controlled Trials (http://controlled-trials.com), Clinical Trials.gov (http://clinicaltrials.gov), and Chinese Clinical Trial Registry (http://www.chictr.org) were also searched. Key words included Alzheimer disease, dementia, cognition, affection, memory dysfunction, hydroxymethylglutaryl-CoA reductase inhibitors, atorvastatin and statins.

DATA SELECTION: Randomized controlled trials of grade A or B according to quality evaluation criteria of the Cochrane Collaboration were selected, in which atorvastatin and placebo were used to evaluate the effects of atorvastatin in the treatment of Alzheimer's disease. Study methodological quality was evaluated based on criteria described in Cochrane Reviewer's Handbook 5.0.1. Revman 5.1 software was used for data analysis.

MAIN OUTCOME MEASURES: Clinical efficacy, safety, withdrawal from the studies, and withdrawal due to adverse effects.

RESULTS: Two randomized controlled trials were included, one was scale A, and the other was scale B. All patients (n = 710, age range 50–90 years) were diagnosed as probable or possible mild to moderate Alzheimer's disease according to standard criteria and treated with atorvastatin 80 mg/d or placebo. There was no difference between the two groups in the final follow-up for Clinical Global Impression of Change scale (*WMD* = 0.13, 95%*CI*: −0.15 to 0.40), the Alzheimer's Disease Assessment Scale-cognitive subscale (*WMD* = 1.05, 95%*CI*: −3.06 to 6.05), Mini-Mental State Examination Scale (*WMD* = 0.77, 95%*CI*: −0.57 to 2.10), and the Neuropsychiatric Instrument (*WMD* = 2.07, 95%*CI*: −1.59 to 5.73). The rates of abnormal liver function, withdrawal from treatment, and withdrawal due to adverse effects were higher in the treatment group (*OR* = 7.86, 95%*CI*: 2.50−24.69; *OR* = 4.70, 95%*CI*: 2.61−8.44; and *OR* = 5.47, 95%*CI*: 3.01−9.94; respectively) compared with the placebo group.

CONCLUSION: There is insufficient evidence to recommend atorvastatin for the treatment of mild to moderate Alzheimer's disease, because there was no benefit on general function, cognitive function or mental/behavior abnormality outcome measures. Efficacy and safety need to be confirmed by larger and higher quality randomized controlled trials, especially for moderate to severe Alzheimer's disease, because results of this systematic review may be limited by selection bias, implementation bias, as well as measurement bias.

Key Words

Alzheimer's disease; dementia; atorvastin; diphosphonate; systematic review; neural regeneration

Abbreviations

AD, Alzheimer's disease; RCTs, randomized controlled trials; *RR*, relative risks; *WMD*, weighted mean difference; *CI*, confidence interval

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline in intelligence, cognitive and memory impairment, and abnormal psychomotor behavior, which commonly affects the elderly[1-3].

Statins, a class of drugs that regulate lipid metabolism, are considered useful for the treatment and prevention of AD, based on their pharmacological properties, which include anti-inflammatory, anti-oxidative, as well as neuroprotective effects[4]. Case-control and cohort studies indicate that statins can reduce the risk of developing dementia[5-6]. However, results have been contradictory regarding the use of statins for the treatment of Alzheimer's dementia[7-11].

In this review, we systematically examine published randomized controlled trials (RCTs) that use atorvastatin to treat AD. A Cochrane system review was conducted to assess the clinical efficacy and safety of atorvastatin for the treatment of AD, with the aim of providing evidence for rational drug use.

DATA AND METHODS

Data retrieval

A search strategy for RCTs recommended by the Cochrane Dementia and Cognitive Improvement Group (http://ims.cochrane.org/) was used in this review. We searched the Cochrane Dementia and Cognitive Improvement Group Specialized Register of trials (May 2011), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2011), Medline (Ovid SP, 1948 to April 2011), Embase (1966 to April 2011), the Chinese Biomedical Literature Database available at http://cbm.imicams.ac.cn (1949 to April 2011), and the Chinese National Knowledge Infrastructure and references lists of articles. No language restrictions were applied. The search concluded in May 2011.

The following key words were used in combination with terms used for AD and atorvastatin: ((Alzheimer disease, Alzheimer$) or (dementia, dement$) or ((cognit$ or memor$ or mental) and (decline$ or impair$ or los$ or deteriorate$))) and ((Hydroxymethylglutaryl-CoA Reductase Inhibitors) or Atorvastatin or statin$.

We also tried to identify ongoing and unpublished trials by searching the following databases: Current Controlled Trials (http://controlled-trials.com), Clinical Trials.gov (http://clinicaltrials.gov), Chinese Clinical Trial Registry (http://www.chictr.org), and by contacting authors of relevant trials.

Inclusion and exclusion criteria

Inclusion criteria: Atorvastatin taken orally at any dose for more than 1 day; randomized double-blind placebo controlled trials comparing atorvastatin with placebo in the treatment of AD; studies graded as scale A or B based on the quality evaluation criteria of Cochrane Reviewer's Handbook 5.0.1; any adult, aged 50 or older, with a diagnosis of probable or possible AD according to one of the following diagnostic criteria: International Classification of Diseases-10, the Chinese Classification of Mental Disorders, American Psychological Association-Diagnostic and Statistical Manual of Mental Diseases, National Institute of Neurological and Communicative Disorders and Stroke-the AD and Related Disorders Association.

Exclusion criteria: Other forms of dementia, such as vascular dementia, Pick's disease, Lewy body disease, and so on; age of patients less than 50; taking or having taken hydroxymethylglutaryl-CoA reductase inhibitors; taking or having taken other drugs for the treatment of AD, such as non-steroidal anti-inflammatory drugs, vitamin E, acetylcholinesterase inhibitors, lecithin or ginkgo.

Quality evaluation and data extraction

Studies were assessed according to criteria for methodological quality described in the Cochrane Reviewer's Handbook 5.0.1 (http://www.cochrane-handbook.org/). Based on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases, methodological quality was evaluated as grade A (low risk of bias), B (moderate risk of bias) or C (high risk of bias). The individual parameters were graded as follows:

(1) Sequence generation—adequate (A), not clear (B) or inadequate (C).

(2) Allocation concealment—adequate (A), not clear (B) or inadequate (C).

(3) Blinding—adequate (A), not clear (B) or inadequate (C).

(4) Incomplete outcome data—based on the effects of the missing data on the study and intention-to-treat (ITT) analysis, it was categorized as adequate (A), not clear (B) or inadequate (C).

(5) Selective outcome reporting—based on the completeness of the results reported, it was categorized into adequate (A), not clear (B) or inadequate (C).

(6) Other biases—based on the study having other biases, it was categorized into adequate (A), not clear (B) or inadequate (C).

Based on these criteria, the studies were subdivided into one of the following three categories:

A: (low risk of bias)—adequately met all quality criteria.

B: (moderate risk of bias)—met one or more of the quality criteria.
C: (high risk of bias)—inadequately met one or more of the criteria.

Outcome measures
Primary measures included clinical efficacy (*i.e*., global function, cognitive function, daily living and behavior) and safety (*i.e*., incidence and severity of adverse effects). Secondary measures included withdrawal from the studies and economic evaluation.

Statistical analysis
We pooled data from trials if they were sufficiently similar using Review Manager (RevMan) (http://ims.cochrane.org/revman/download). Statistical heterogeneity was tested using the chi square statistic. With the I^2 statistic greater than 50%, $P > 0.10$ for intra-subgroups and $P > 0.05$ for inter-subgroups was considered evidence of substantial heterogeneity. It is appropriate to pool data even when heterogeneity is detected, with the random-effects model being used instead of fixed-effects. Potential sources of heterogeneity were explored using subgroup and sensitivity analyses. Relative risks (*RR*) were used for binary data and the weighted mean difference (*WMD*) was used for continuous data, which were described using a 95% confidence interval (*CI*). Publication bias was tested using the funnel plot or another corrective analytical method, depending on the number of clinical trials included in the assessment.

RESULTS

Data retrieval
A total of 264 articles were retrieved which were published between 2000 and 2011, and 254 were excluded after screening the titles and abstracts because the study purpose was not consistent with the systematic evaluation or animals were involved in the studies. Eight studies were further excluded because of duplicate publication in 4, un-matched intervention in 2[9, 12], different research purposes in 1[13], and graded as C in 1[10]. Therefore, 2 RCTs reported in English were finally included in the meta-analysis[7-8] (Figure 1). The study sites were located abroad.

Baseline analysis and quality evaluation
Two randomized placebo-controlled trials were identified. The study of Sparks *et al* [7] is a single-center RCT study, and the study of Feldman *et al* [8] is multi-center. The studies were conducted to compare atorvastatin at 80 mg/d with placebo for the treatment of mild to moderate AD (Mini Mental State Examination (MMSE) score more than 12). The intervention periods were 50 weeks and 80 weeks for the studies of Sparks *et al* [7] and Feldman *et al* [8], respectively. Patients in the study of Feldman *et al* [8] received donepezil 10 mg for at least 3 months before randomization, while participants in the other study[7] were allowed to continue the use of stable doses of medications for the treatment of AD. A total of 710 patients were diagnosed as probable or possible AD (as they met the criteria described by the National Institute of Neurological and Communicative Disorders and Stroke, the Alzheimer's Disease and Related Disorders Association, and the Diagnostic and Statistical Manual of Mental Diseases-IV). Of these, 63 and 614 cases were included in ITT analysis for intervention assessment, while 63 and 639 cases were included in safety assessment, from the studies of Sparks *et al* [7] and Feldman *et al* [8], respectively. Details of these studies are shown in Table 1.

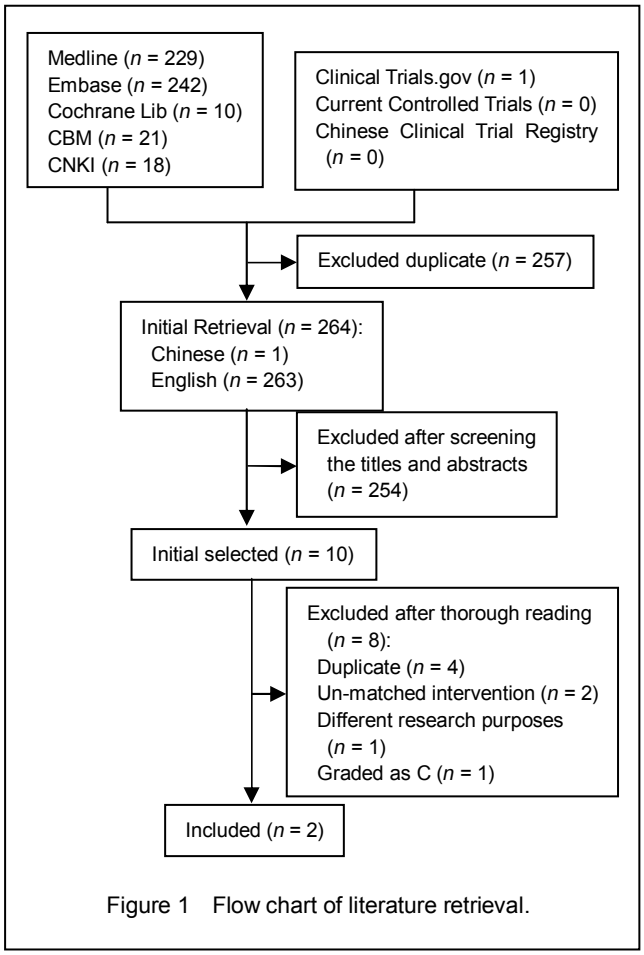

Figure 1 Flow chart of literature retrieval.

The study of Feldman *et al* [8] was scale A, and that of Sparks *et al* [7] was scale B (Table 2). Publication bias was not tested, because only two RCTs were included in the meta-analyses. The two studies were assessed for adequate randomization, allocation concealment and blinding, and ITT analysis was used.

Table 1 Characteristics of included studies using atorvastatin for the treatment of Alzheimer's disease

Included studies	Country	Study design	Cases (*n*/*n*)	Patient (control/placebo)			Intervention		Outcome measures	Study period
				Age (year)	Gender (female%)	Drug before random allocation	Atorvastatin	Placebo		
Sparks *et al* [7]	USA	RCT	32/31	78.2±1.3/ 78.9±1.2	35.5/37.5	CHEI ≥ 3 mon (29/28)	Atorvastatin (80 mg/d)	Placebo	ADAS-cog, CGIC, GDS, MMSE, NPI, ADCS-ADL	52 wk
Feldman *et al* [8]	UK and other 10 countries	Multicenter RCT	297/317	74.0±8.0/ 73.2±8.7	53/51	Donepezil 10 mg/d ≥ 3 mon (297/317)	Atorvastatin (80 mg/d) Donepezil (10 mg/d)	Placebo+ Donepezil (10 mg/d)	ADAS-cog, CGIC, NPI, MMSE, CDR-SB, ADFACS	72 wk + atorvastatin 8 wk

CHEI: Cholinesterase Inhibitors; ADAS-Cog: the Cognitive Subscale of Alzheimer disease assessment scale; CGIC: Clinical Global Impression of Change scale; GDS: the Geriatric Depression Scale; MMSE: Mini-Mental State Examination Scale; NPI: the Neuropsychiatric Inventory; ADCS-ADL: Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory; CDR-SB: the Clinical Dementia Rating-sum of the Boxes Score; ADFACS: Alzheimer disease Functional Assessment and Change Scale; RCT: randomized controlled trial; mon: month; wk: week.

Table 2 Quality of included studies using atorvastatin for treatment of Alzheimer's disease

Included studies	Sequence	Allocation concealment	Blinding	Incomplete outcome data	Elective outcome reporting	Other bias	Category
Sparks *et al* [7]	Adequate (Excel, block randomization)	Adequate (controled by pharmacy)	Adequate (valuator, patient)	Adequate (lost to follow-up, ITT)	Unclear (uncompleted reported of complication)	Unclear	B
Feldman *et al* [8]	Adequate (center random)	Adequate (series offered by center)	Adequate (valuator, patient)	Adequate (lost to follow-up, ITT)	Adequate (completed reported)	None	A

ITT: Intention-to-treat analysis.

Furthermore, last squared counted last-observation-carried-forward (LOCF) was also reported in the two studies. Expected results were reported in the study of Feldman *et al* [8] with no other bias. Adverse events were reported incompletely in the study of Sparks *et al* [7], and patient withdrawal from the study were not included in analysis for adverse effects.

Zhao *et al* [9] evaluated the effect of atorvastatin for the treatment of moderate to severe AD compared with combined memantine. The study assigned groups using random number table 1:1, while allocation concealment and blinding were not reported, and ITT analysis was not used. Thus, the study was judged as scale C for methodological quality, and was consequently excluded.

Meta analysis

Evaluation indexes

Global function: Clinical Global Impression of Change scale rated from 1 to 7 (significant, moderate, minimal, and no improvement; minimal, moderate, and significant aggravation) were used as clinical global measures in these two studies.

Cognitive function: The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and MMSE were used as cognitive function measures in these two studies. ADAS-Cog comprises 11 individual tests, including spoken language (5 tests), memory (3 tests), orientation (1 test) and habituation (2 tests). The total score ranges from 0–70. High score indicates greater impairment. MMSE, the score, ranging from 0 (severe impairment) to 30 (normal), evaluates cognition in eight areas-orientation (10 points), immediate recall (6 points), attention (5 points), multi-step task (3 points), naming objects (2 points), repetitive tasks (1 point), literacy (2 points), and visual guidance (1 point).

Activities of daily living: Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) was used in the Alzheimer's Disease Cholesterol-Lowering Treatment trial in 2005, while Alzheimer disease Functional Assessment and Change Scale (ADFACS) was used in LEADe 2010. Total score in ADCS-ADL ranged from 8 to 24 points, and included eight items (cook, wear, wash, sit down and stand up/go to or get out of bed, indoor walking, and go to stool, urine and stool control, and bathing). ADFACS is a 16-item scale assessing four different abilities-household appliances use, letter handwriting, habit, and shopping-in patients with mild to moderate dementia. Total score ranges from 0 to 54 (no impairment).

Behavioral disturbance: The Neuropsychiatric Instrument, a 12 item scale, was used in the two RCTs to evaluate behavioral and neuropsychiatric symptoms, including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behavior, night-time behavior, and appetite/eating disorder. The

scores range from 12 to 144, and are based on frequency and severity, and are assessed by caregivers. A low score indicates improvement.

Safety: Feldman *et al* [8] examined withdrawal, adverse events, adverse effects, and death. Sparks *et al* [7] only reported adverse events related to withdrawal.

Effects of intervention

Global function detection: Clinical Global Impression of Change Scale was used as a clinical global measure in these two studies. The random effects model was used, because there was statistical heterogeneity in these studies. There was no evidence of benefit associated with atorvastatin use, at either 9 months (*WMD* = 0.12, 95%*CI*: −0.22 to 0.46) or at the final follow-up (*WMD* = 0.13, 95%*CI*: −0.15 to 0.40; Figure 2).

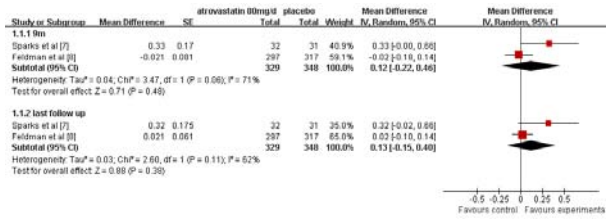

Figure 2 Results of Clinical Global Impression of Change scale between atorvastatin (80 mg/d) and placebo for treatment of mild to moderate Alzheimer's disease.

There was no statistical difference at 9 months or at the final follow-up ($P > 0.05$).

When the data from Sparks *et al* [7] were excluded from the sensitivity analyses, there was no substantial change in the results.

Cognitive function detection: Both studies used ADAS-cog and MMSE as cognitive function measures. The random effects model was used, because there was statistical heterogeneity in these studies. There was no evidence of benefit associated with atorvastatin use on ADAS-cog or MMSE (Figures 3, 4). When the data from Sparks *et al* [7] was excluded from the sensitivity analyses, there was no substantial change in the results.

ADAS-cog: *WMD* = 1.05, 95%*CI*: −3.06 to 6.05. MMSE: at 24 weeks, *WMD* = −0.52, 95%*CI*: −0 .51 to 1.55; at 52 weeks, *WMD* = 0.77, 95%*CI*: −0.57 to 2.10.

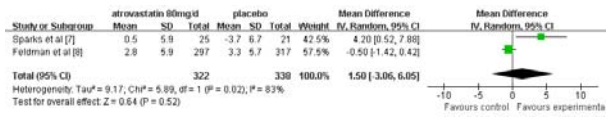

Figure 3 Results of Alzheimer's Disease Assessment Scale-cognitive subscale between atorvastatin (80 mg/d) and placebo for treatment of mild to moderate Alzheimer's disease.

There was no statistical difference between atorvastatin and placebo ($P > 0.05$).

Activities of daily living: ADCS-ADL showed no significant differences between atorvastatin and placebo groups in Sparks *et al* [7]. There was no evidence of benefit associated with atorvastatin using ADFACS in Feldman *et al* [8] (*MD* = 0.043, 95%*CI*: −1.24 to 1.42; ITT-LOCF).

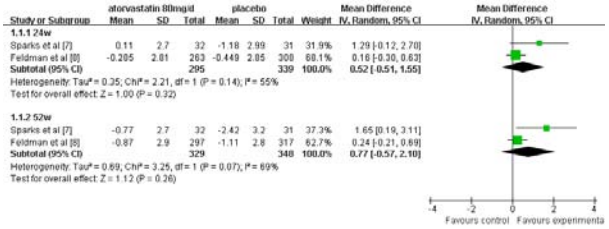

Figure 4 Results of Mini Mental State Examination between atorvastatin (80 mg/d) and placebo for treatment of mild to moderate Alzheimer's disease.

There was no statistical difference at 24 or 52 weeks between atorvastatin and placebo ($P > 0.05$).

Behavioral disturbance: The Neuropsychiatric Inventory (NPI) was used to assess behavioral disturbances in the two studies. The random effects model was used, because there was statistical heterogeneity in the meta-analyses. There was no evidence of benefit associated with atorvastatin, at either 24 weeks (*WMD* = 2.28, 95%*CI*:−1.92 to 6.47) or at 52 weeks (*WMD* = 2.07, 95%*CI*: −1.59 to 5.73; Figure 5). When data from Sparks *et al* [7] was excluded from the sensitivity analyses, there was no substantial change in the results.

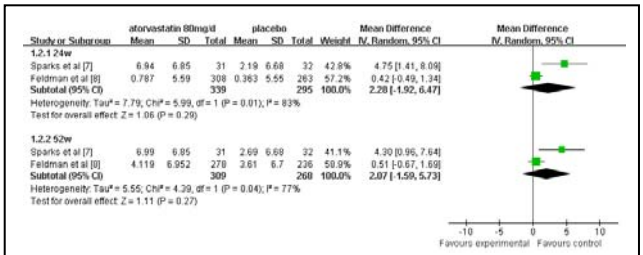

Figure 5 Results of Neuropsychiatric Inventory between atorvastatin (80 mg/d) and placebo for treatment of mild to moderate Alzheimer's disease. There was no statistical difference at 24 or 52 weeks between atorvastatin and placebo ($P > 0.05$).

Safety

A total of 346 cases in the atorvastatin group and 356 cases in the placebo group of adverse events were reported in the meta-analyses. Feldman *et al* [8] reported 272 (86.6%, 1 134) and 277 (85.2%, 1 247) cases of adverse events in the atorvastatin and placebo groups, respectively. They also reported 103 (32.8%) and 61 (18.8%) cases of adverse effects in the atorvastatin and placebo groups, respectively. There were significant differences (*OR* = 2.08, 95%*CI*: 1.46–2.97). Sparks *et al* [7] only reported adverse events related to withdrawal.

Severe adverse effects, abnormal liver function, withdrawal, and death were reported in both studies. The Peto odds ratio was used in these meta-analyses. The meta-analyses of severe adverse effects showed no significant differences between atorvastatin and placebo groups (7/3 atorvastatin/placebo, *OR* = 2.31, 95%*CI*: 0.66–8.04). The meta-analyses of abnormal liver function showed significant differences between atorvastatin and placebo groups (12/0 atorvastatin/placebo, *OR* = 7.86, 95%*CI*: 2.50–24.69). The meta-analyses of total withdrawal, withdrawal for treatment, and withdrawal for adverse effects showed significant differences between atorvastatin and placebo groups (withdrawal: *OR* = 1.45, 95%*CI*: 1.05–2.01; for treatment: *OR* = 4.70, 95%*CI*: 2.61–8.44; for adverse effects: *OR* = 5.47, 95%*CI*: 3.01–9.94). The meta-analyses of death showed no significant difference between the atorvastatin and placebo groups (9/7 atorvastatin/placebo, *OR* = 1.33, 95%*CI*: 0.49–3.58), and there was no association between death and treatment. When data from Sparks *et al* [7] was excluded from the sensitivity analyses, there was no substantial change in the results.

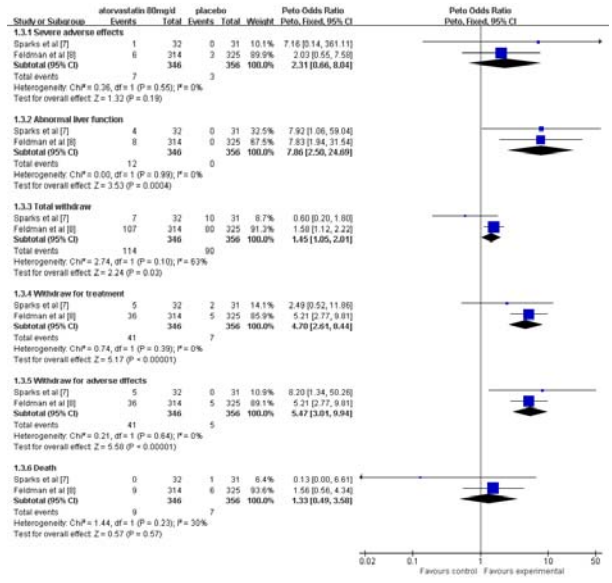

Figure 6 Results of safety evaluation between atorvastatin (80 mg/d) and placebo for treatment of mild to moderate Alzheimer's disease.

Statistically significant differences ($P < 0.05$) were present for the incidence of severe adverse effects, total withdrawal, withdrawal for adverse effects and withdrawal for treatment at 24 and 52 weeks, but not in the rate of mortality.

DISCUSSION

Research quality evaluation

Adequate sequence generation, allocation concealment, and blinding were present in the two RCTs, and ITT was used in both studies, decreasing selection bias, implement bias and measurement bias. Adverse effects not related to withdrawal were not reported, and four patients who withdrew after random allocation were not included in the analysis of adverse events by Sparks *et al* [7], so follow-up bias and reporting bias was likely to have been present. Thus, the data from Sparks *et al* [7] was excluded from the sensitivity analysis. Additionally, concomitant medications and the use of different evaluation indexes in these studies made analysis difficult, which impacted on the conclusion and clinical applicability of this systematic review.

Efficacy analysis

An association between high serum cholesterol levels and increased susceptibility to AD has been reported. High serum cholesterol levels are associated with learning impairment and cognitive decline in AD[14]. Consequently, statins, which lower cholesterol levels, are regarded as useful drugs for the treatment and prevention of AD. In addition, statins have anti-inflammatory, anti-oxidative and neuroprotective actions[4]. β-amyloid peptide (Aβ) can induce neural degeneration, and it has been shown that lower blood plasma $A\beta_{42/40}$ levels are associated with abnormal cognitive function in the elderly[15]. Statins can decrease serum Aβ and cerebrospinal fluid $A\beta_{40}$ concentrations in AD[9, 16], as well as decrease the number of neurofibrillary tangles, which are pathognomonic brain lesions in AD[17]. Although some reports have claimed that statins play an important role in the treatment and prevention of AD, systematic reviews have confirmed that statins cannot reduce the risk of developing AD among the elderly[18]. A systematic review, comprising the studies of Feldman *et al* [8] and Sparks *et al* [7], as well as an RCT examining the use of simvastatin for the treatment of AD (Simons *et al* [9]), was performed in 2010 to assess the effect of statins in the treatment of AD[19]. There was no significant difference between statins and placebo in the treatment of AD in the meta-analysis[19], although improved MMSE performance in the statin group was shown in the study of Simons *et al* [9]. Clinical heterogeneity has to be addressed when combining the results of these studies, because atorvastatin has a stronger ability to lower cholesterol levels than simvastatin. Consequently, meta-analysis is not suitable to combine the data in the absence of subgroup analysis. Thus, we conducted this meta-analysis to assess the clinical efficacy and safety of atorvastatin in the treatment of AD, based on a systematic and exhaustive search of the published literature.

Our present systematic review comprised two RCTs involving a total of 710 outpatients from 10 European

countries, the United States and South Africa to compare atorvastatin at 80 mg/d with placebo in the treatment of mild to moderate AD. The meta-analysis showed that there was no difference between the groups based on global function, cognitive function and behavior. Different scales were used in these studies to assess daily living, but statistical difference was not detected. The study of Zhao *et al* [10], comparing combined atorvastatin and memantin with memantin for the treatment of moderate to severe AD, was excluded due to poor quality. A study conducted by Sano *et al* [12] will be helpful to explore the effect of atorvastatin for the treatment of AD.

In this meta-analysis, the rate of severe adverse effects and mortality were not statistically different between atorvastatin and placebo. However, there were significant differences between the two groups in the number of of adverse effects and adverse events, as well as in liver function. Compared with the placebo group, higher rates of withdrawal, withdrawal for treatment and adverse effects were present in the atorvastatin group. A similar result for withdrawal from studies was shown in McGuinness 2009[18] which involved 26 340 patients, while opposite results were shown in McGuinness 2010[19] involving 683 patients. In McGuinness 2010, meta-analysis involved a smaller sample size and shorter follow-up. Therefore, a systematic review aiming to assess the adverse effects of statins should be conducted.

Limitations of this systematic review

Complete and comprehensive retrieval strategies were formulated and implemented, including retrieving papers by computer, manually retrieving conference reports, searching clinical trial registries, and contacting authors and drug manufacturers for relevant trials. Negative results were also considered, minimizing reporting bias. However, retrieval languages were limited to Chinese and English, so publication bias was likely present. Heterogeneity was present in the meta-analysis, because of different combined intervention or a small sample in all curative effect scales. Means and *P* values were reported in Sparks *et al* [7], and means, 95% *CI*, standard error and *P* values were reported in Feldman *et al* [8]. Standard deviations were calculated in both studies according to the methods of Kirwan *et al* [20], which may affect the results of meta-analysis. In addition, this systematic review only evaluated the effects of atorvastatin in the treatment of mild to moderate AD, which is not suitable for other drugs or for moderate to severe AD. Adverse events and adverse effects may not be completely described in studies included in this meta-analysis, because the sample sizes were small and the follow-up period was short. Therefore, larger sample sizes and longer follow-up are needed to confirm the results of this review.

Conclusion

There is insufficient evidence to recommend atorvastatin for the treatment of mild to moderate AD, and no benefit on critical outcome measures (*i.e*., Clinical Global Impression of Change Scale, ADAS-Cog, MMSE and NPI) was observed. Well-designed multi-center randomized controlled trials, with a large sample size, should be conducted to evaluate the effects of atorvastatin on mild to moderate AD. Such studies would need to be confirmed by high quality RCTs with large sample sizes, especially for moderate to severe AD.

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Author contributions: Shuyan Chen designed this study and guided manuscript writing. Yuan Sun designed this study, retrieved literature, conducted statistical analyses and wrote the manuscript. Genfa Wang and Zhihong Pan extracted data.

Conflicts of interest: None declared.

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