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REVIEW

Alpha lipoic acid combined with epalrestat: a therapeutic option for patients with diabetic peripheral neuropathy

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Background: Alpha lipoic acid (ALA), a type of antioxidant, is used in combination with epalrestat in the treatment of diabetic peripheral neuropathy (DPN). However, whether combined treatment is superior to epalrestat monotherapy is controversial.

Methods: We conducted a systematic search of PubMed, Cochrane Library and Chinese databases to identify all randomized controlled trials (RCTs) up to October 31, 2017. Data were extracted to evaluate methodological quality and analyzed using Review Manager 5.3.0 software.

Results: Twelve studies were included. Compared to epalrestat monotherapy, ALA 600 mg/d once a day (qd) combined with epalrestat 50 mg three times a day (tid) augmented the total effectiveness rate (14 days – risk ratio [RR]: 1.40, 95% CI: 1.16–1.69, P=0.0005; 28 days – RR: 1.48, 95% CI: 1.27–1.72, P<0.00001); at the same, it could improve the median motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV), peroneal MNCV, and SNCV after 14, 21, and 28 days of treatment and could reduce the Toronto Clinical Scoring System (TCSS) (weighted mean difference [WMD]: −1.60, 95% CI: (−2.91, −0.29), P=0.02) and Total Symptom Score (TSS) (WMD: −0.93, 95% CI: −1.27, −0.60, P<0.00001) after 21 days of treatment. The treatment strategy of ALA 300 mg/d qd combined with epalrestat 50 mg tid had the same effects in regard to the total effectiveness rate (RR: 1.37, 95% CI: 1.18–1.59, P<0.0001), median MNCV (WMD: 6.12, 95% CI: 5.04, 7.20, P=0.00001), median SNCV (WMD: 6.70, 95% CI: 5.75, 7.65, P=0.00001), peroneal MNCV (WMD: 6.68, 95% CI: 5.82, 7.55, P=0.00001), and peroneal SNCV (WMD: 4.27, 95% CI: 3.34, 5.20, P=0.00001) after 28 days of treatment.

Conclusion: ALA combined with epalrestat is an effective option for DPN patients. Future large-sample RCTs should be conducted to further confirm this finding.

Keywords: alpha lipoic acid, diabetic peripheral neuropathy, epalrestat, meta-analysis

Introduction

Diabetic neuropathy (DN) is a very common, symptomatic, long-term complication of diabetes mellitus, affecting nearly 50% of patients with type 1 and/or type 2 diabetes.[1] According to International Diabetes Federation data, ~592 million people worldwide will be diagnosed with diabetes by 2035.[2] DPN affects ~236 million people, primarily in low- and middle-income countries, causing a very large financial burden.[3,4] Diabetic peripheral neuropathy (DPN) is closely associated with high morbidity, mortality, and diminished quality of life.[5] Diabetic damage due to hyperglycemia and metabolic imbalance – primarily, oxidative stress – may appear in the neurons (axons or myelin sheaths) of DPN patients.[6] Therefore, the typical clinical manifestations of DPN are

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tingling, burning, pain, cramps, paresthesia, and numbness.[3] With regard to oxidative stress and the related pathways, some drugs, such as alpha lipoic acid, aldose reductase inhibitors (ARIs; eg, epalrestat), and protein kinase C inhibitors, are being investigated.[6] These drugs have been widely used to treat DPN in clinical or intensive long-term comparative trials.

Nerve conduction velocity (NCV) is an objective indicator of neuronal damage in the distal segment of the peripheral nerves and is accepted as an essential part of the diagnosis of DPN.[7–9] Previous studies have shown that motor nerve conduction velocity (MNCV) or sensory nerve conduction velocity (SNCV) are significantly reduced with the development of DPN.[10,11] ALA – a coenzyme in the tricarboxylic acid cycle – is an antioxidant that may prevent and reduce diabetic micro- and macrovascular complications[12] and is an effective treatment of DPN.[13] Experimental studies have proved that ALA can improve nerve blood flow, reduce oxidative stress, and improve distal nerve conduction.[14] One meta-analysis reported that infusions of ALA (600 mg IV/day) ameliorated the symptoms of neuropathy after 3 weeks,[15] with IV therapy being more effective than oral treatment (SMD =–2.8 vs SMD =–1.8).[16] Epalrestat is an ARI that relieves oxidative stress and suppresses the polyol pathway, which delays the progression of DPN and effectively and safely improves both DN symptoms and the MNCV in the context of neuropathy.[17–19]

Accumulating evidence has shown that ALA combined with epalrestat may be a viable option for patients with DPN because of its marked beneficial effect on clinical symptoms and nerve conduction velocity (NCV).[20] However, the available randomized controlled trials (RCTs) examining this combination therapy have not been systematically retrieved and evaluated. We conducted a meta-analysis to assess the efficacy and safety of ALA combined with epalrestat for patients with DPN.

Materials and methods

This systematic review was registered in PROSPERO CRD42017081310, and we strictly followed the Cochrane Collaboration framework guidelines[21] and the PRISMA Statement[22] to conduct the review (Table S2).

Selection criteria

Studies that satisfied the following criteria were selected. 1) Patients: Patients with DPN. The diagnostic criteria for diabetes mellitus and its complications in the trials were in accordance with the criteria of the 1999 World Health Organization (WHO) guideline.[23] The diagnostic criteria for DPN were in accordance with a statement by the American Diabetes Association[24] or the guidelines for the prevention and treatment of Type 2 diabetes (2013 version) of the Chinese Diabetes Society.[25] Patients with other types of peripheral neuropathy, such as cerebral infarction, Guillain–Barre syndrome, severe venovascular disease, cervical spondylosis, and lumbar lesions, were excluded. There were no restrictions on patient race, region, age, sex, or on the severity or duration of DPN. 2) Interventions: Combined treatment was compared to epalrestat monotherapy or on the basis of co-intervention for the treatment of DPN patients. 3) Comparisons: Subjects received ALA combined with epalrestat vs epalrestat alone. 4) Outcomes: Clinical effectiveness rate, Toronto Clinical Scoring System (TCSS), Total Symptom Score (TSS), adverse reactions, MNCV, and SNCV were measured. The total effectiveness rate was calculated on the basis of following criteria: subjective symptom alleviated, tendon reflex improved, and NCV increased by ≥3 m/s after treatment. 5) Study design: RCTs that determined the clinical utility of ALA combined with epalrestat for the treatment of DPN were selected. Reviews, cross-sectional studies, cohort studies, animal experiments, and commentaries were excluded.

Search strategy

A systematic literature search of multiple databases for relevant trials was undertaken. All Chinese databases, including the Chinese Biomedical Database, Wanfang Data, the VIP Chinese Science and Technology Journals Database, the China National Knowledge Infrastructure, as well as English databases, such as PubMed and Cochrane Library, were searched from their inception to October 31, 2017. For the Chinese databases, free-text terms such as "epalrestat" or "lipoic acid" and "diabetic peripheral neuropathy" or "peripheral neuropathy" or "diabetic neuropathy" or "DPN" and "randomized controlled trial" or "randomized" and "blind" were used; there were no restrictions on subheadings. For the English databases, the following mesh terms were used, with no restriction on subheadings: ((diabetic AND peripheral neuropathy) OR (diabetic neuropathy OR diabetic peripheral neuropathy)) AND ((thioctic acid) OR (thioctic AND acid) OR (lipoic acid) OR (lipoic AND acid)) AND (epalrestat) AND (randomized OR randomized controlled trial) AND blind. The search strategies of PubMed and CNKI were showed in Table S1. Other electronic databases will be search using the similar strategy. Publication languages were confined to Chinese and English. Clinical trials published in abstract form were selected only if sufficient

data could be retrieved from the abstract or authors. The reference lists of the potentially eligible studies were also reviewed to discover additional clinical trials missed by the initial search.

Data selection

All retrieved results were imported into NoteExpress 3.2.0. Duplicate data from different databases were identified by NoteExpress 3.2.0, and two reviewers (Wang XT and Lin HX) independently screened the remaining abstracts and full texts of potentially eligible trials. Any disagreements were settled by discussion among four authors (Wang XT, Lin HX, Jin YL and Zhang R). SX checked the final data set. Treatment strategies that were not repeated were eliminated.

Data extraction and risk of bias

For each eligible study, two reviewers (Wang XT and Lin HX) extracted study information (first author names, publication year), patient data (age, sample sizes of the treatment group and control group), therapeutic strategy (intervention methods, intervention time), and DPN outcome. Risk assessment and quality evaluation, as determined by the Cochrane criteria, were used to evaluate each eligible study.[26]

Statistical analysis

The clinical effectiveness rate, TCSS, TSS, adverse reactions, MNCV, and SNCV were evaluated and merged. Review Manager (version 5.3.0) software was utilized to analyze the data. The data are presented as RR or weighted mean difference (WMD) and 95% CI for the included studies. Statistical heterogeneity was assessed using the Chi-squared test and I^2 values.[27] $I^2>75\%$ indicated significant heterogeneity, $50\% < I^2 \leq 75\%$ was regarded as mildly significant heterogeneity, and $0\% \leq I^2 \leq 50\%$ was defined as indicating no heterogeneity. A random-effects model and sensitivity analysis was undertaken when mild or significant heterogeneity ($P<0.05$, $I^2>50\%$) was detected among the analyzed studies. Moreover, subgroup analysis was conducted on the basis of different therapeutic methods or follow-up durations. A fixed-effects model was used in the absence of heterogeneity. When possible, comparisons of studies that used the same treatment strategy for different durations were made using the chi-squared test and the associated P-value. Funnel plots, Begg's test, and Egger's test were conducted on clinical outcomes to further analyze the potential publication bias. Begg's test $P>0.05$ and Egger's test $P>0.05$ indicated no significant publication bias.

Results

Eligible studies

Our initial search strategy yielded 240 potential articles, and Figure 1 shows the search process. Duplicate records were removed in NoteExpress 3.2.0 (n=135), and 59 studies were excluded after screening of the titles and abstracts. The full

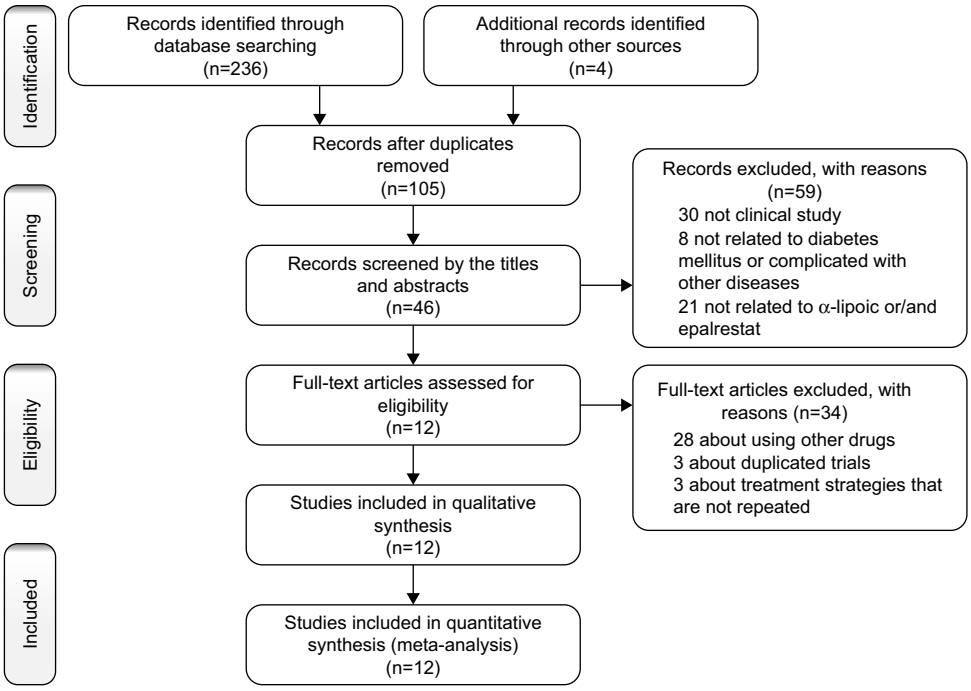

Figure 1 Flow chart of the search process.

text of 46 studies was screened. Twenty-eight trials using other drugs, three trials with suspected duplicated data, and three trials[28–30] that did not use the same treatment strategy were removed. Twelve clinical trials were included in the meta-analysis. The detailed characteristics of the included studies are presented in Table 1.

Risk of bias of the included studies

The quality of the included studies was high in terms of randomization, completeness of outcome data, selective reporting, and other potential biases. However, the studies conducted by Fang[32] and Huang[41] did not mention a randomized design. In addition, the poor allocation concealment, inadequate blinding of participants or personnel, and inadequate blinding of outcome assessment should be considered (Figure 2).

Total effectiveness rate

Eight studies containing total effectiveness rate data were included. The meta-analysis was conducted using a fixed-effects model based on the lack of heterogeneity (I^2=0%, P>0.05). According to the subgroup analysis, although the total effectiveness rate differed by treatment strategy, the combined treatment exhibited a better total effectiveness rate than epalrestat alone (ALA 600 mg/d qd combined with epalrestat 50 mg tid for 14 days – RR: 1.40, 95% CI: 1.16–1.69, P=0.0005; for 28 days – RR: 1.48, 95%

Table 1 Characteristics of the included studies

Study	Year	Age/years EG/CG	Number EG/CG	Intervention methods		Intervention time (days)		Outcomes
				EG	CG	Lipoic acid	Epalrestat	
He et al[31]	2013	82±5/82±5	36/35	CG + ALA 300 mg, IV qd	Epalrestat 50 mg, PO, tid	28	28	NCV, clinical effects, adverse reactions, the function of liver and renal, hemanalysis, urinalysis, dynamic electrocardiogram
Fang[32]	2014	52.8±12.7/52.8±12.7	30/30	CG + ALA 600 mg, IV qd	Epalrestat 5 mg, PO, tid	14	14	NCV, clinical effects, adverse reactions, the function of liver and renal, FPG, PBG
Liu[33]	2014	56.8±5.4/55.2±6.8	24/24	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	28	28	NCV, clinical effects
Yan[34]	2015	54.8±9.3/54.8±9.3	24/24	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	21	21	NCV, TCSS, TSS
Qu and Zeng[35]	2009	58.6±8.7/58.6±8.7	25/25	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	28	28	NCV, clinical effects, adverse reactions
Deng[36]	2011	45~72/45–72	43/43	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	28	28	NCV, clinical effects
Luo et al[37]	2013	57±13/57±13	40/40	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	14	14	NCV, clinical effects
Han[38]	2012	63±6/63±5	55/55	CG + ALA 300 mg, IV qd	Epalrestat 50 mg, PO, tid	28	28	NCV, clinical effects, adverse reactions, EMG, NSS, MDNS
Wang et al[39]	2013	60.1±10.5/57.3±11.2	41/41	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	21	21	NCV, clinical effects, adverse reactions, TCSS, TSS
Yang and Zhang[40]	2012	58.3±8.8	50/50	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	28	28	Clinical effects, adverse reactions
Huang[41]	2016	54.2±2.7/54.8±2.5	29/29	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	21	21	NCV, clinical effects, adverse reactions, TCSS, TSS
Qi[42]	2016	58.01±7.73/57.31±6.79	30/30	CG + ALA 600 mg, IV qd	Epalrestat 50 mg, PO, tid	21	21	NCV, clinical effects

Abbreviations: EG (experimental group), the group administered lipoic acid combined with epalrestat; CG (control group), the group administered lipoic acid monotherapy; ALA, α-lipoic acid; qd, once a day; IV, intravenous injection; PO, oral administration; tid, three times a day; NCV, nerve conduction velocity; EMG, electromyography; TCSS, Toronto Clinical Scoring System; TSS, Total Symptom Score; NSS, Neurological Symptom Score; MDNS, Michigan Diabetic Neuropathy Score; FPG, fasting plasma glucose; PBG, postprandial blood glucose.

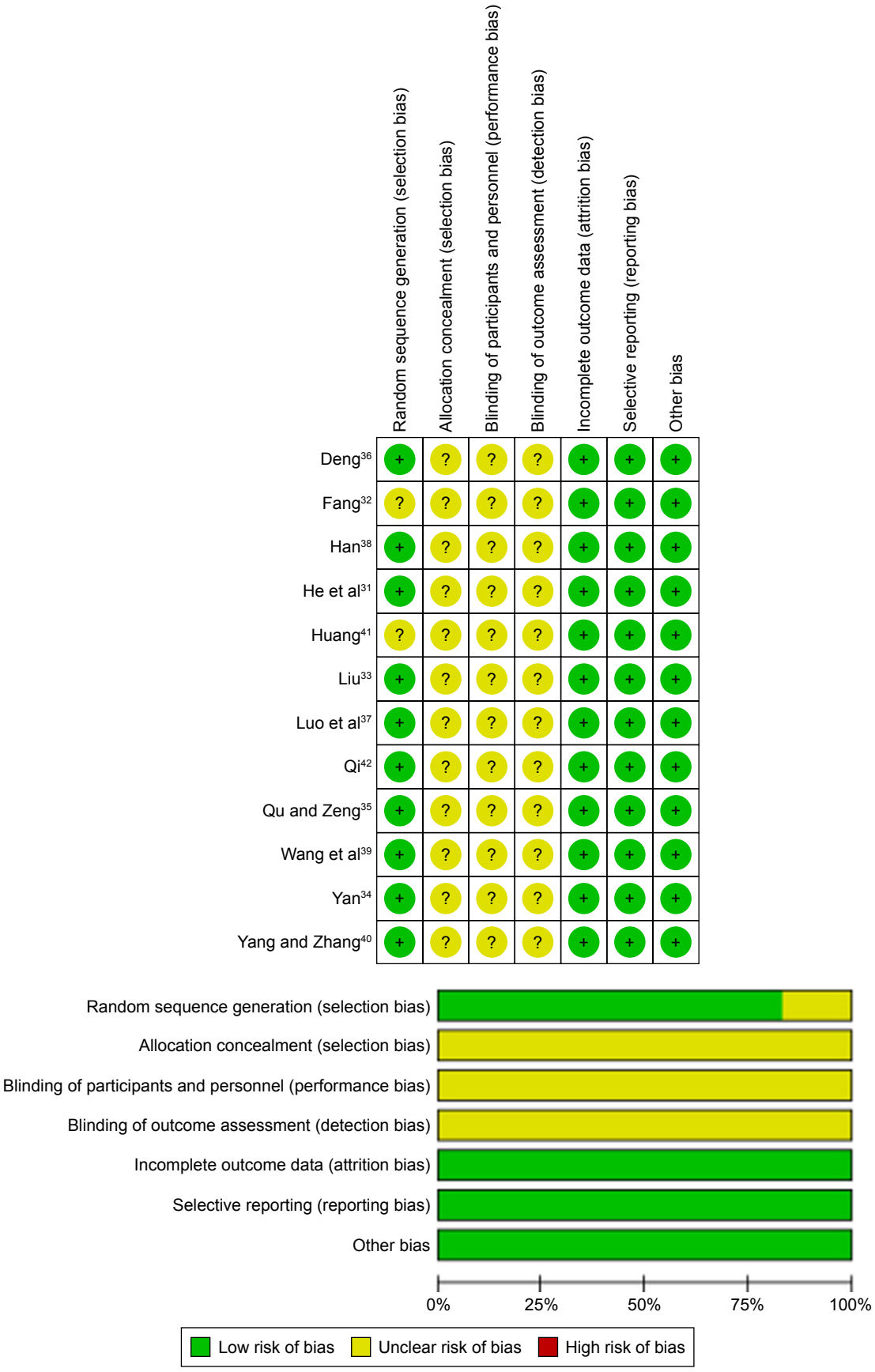

Figure 2 Risk of bias graph and bias summary.

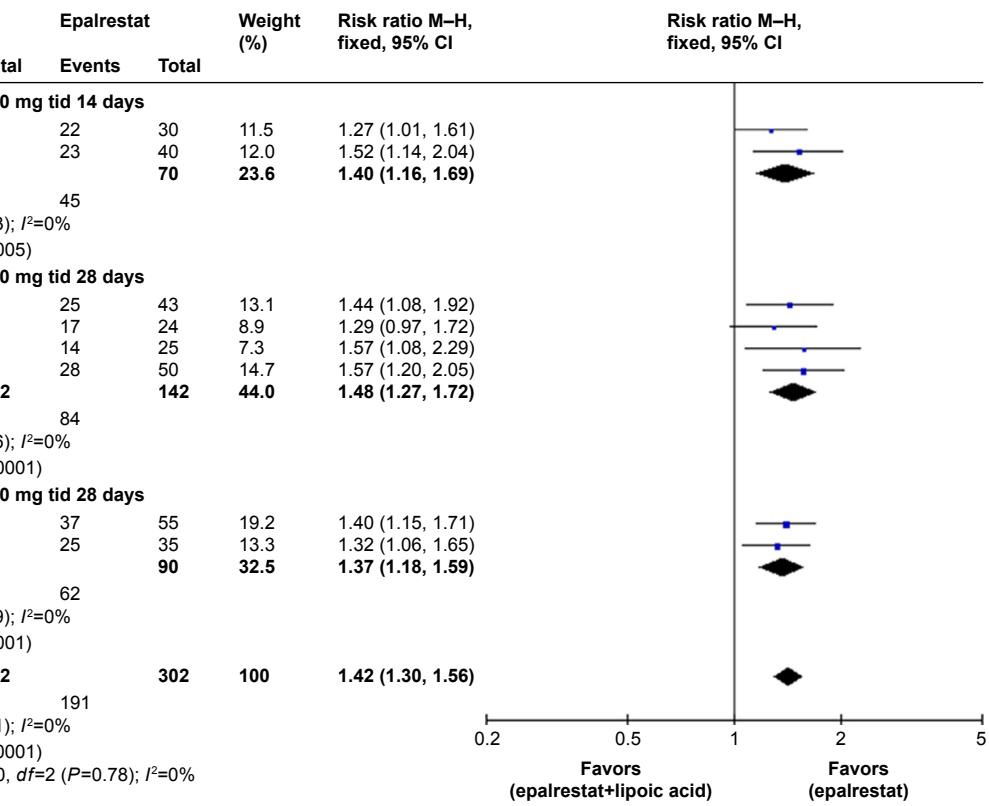

Figure 3 Forest plot of meta-analysis of total effectiveness rate.
Abbreviations: M–H, Mantel–Haenszel; qd, once a day; tid, three times a day.

CI: 1.27–1.72, $P<0.00001$; ALA 300 mg/d qd combined with epalrestat 50 mg tid for 28 days – RR: 1.37, 95% CI: 1.18–1.59, $P<0.0001$; Figure 3).

Median MNCV

Ten trials investigated the median MNCV. A beneficial and statistically significant effect of combined treatment on median MNCV was observed in two different treatment strategies compared with epalrestat monotherapy. The pooled results of ALA 600 mg/d qd combined with epalrestat 50 mg tid were significantly higher than that of epalrestat monotherapy (14 days – pooled WMD: 7.98, 95% CI: 6.17–9.80, $P<0.00001$; 21 days – WMD: 2.74, 95% CI: 1.50–3.98, $P<0.0001$; 28 days – WMD: 9.01, 95% CI: 3.46–14.56, $P=0.001$). Significant differences were identified between these different treatment durations ($\chi^2=24.41$, $P<0.00001$). Moreover, ALA 300 mg/d qd combined with 50 mg tid epalrestat for 28 days indicated the benefit of the combined-treatment regimen (WMD: 6.12, 95% CI: 5.04–7.20, $P<0.00001$; Table 2).

Peroneal MNCV

Eleven trials investigated peroneal MNCV. The pooled results suggested a significant difference in peroneal MNCV between the combined treatment and epalrestat-alone groups in two different treatment strategies (ALA 600 mg/d qd combined with epalrestat 50 mg tid: for 14 days – WMD: 9.77, 95% CI: 7.78–11.75, $P<0.00001$; for 21 days – WMD: 4.18, 95% CI: 1.49–6.88, $P=0.002$; for 28 days – WMD: 7.13, 95% CI: 3.94–10.32, $P<0.0001$. ALA 300 mg/d qd combined with epalrestat 50 mg tid for 28 days – WMD: 6.68, 95% CI: 5.82–7.55, $P<0.00001$; Table 2). There were significant differences between the results obtained using ALA 600 mg/d qd combined with epalrestat 50 mg tid for different durations ($\chi^2=10.84$, $P=0.004$).

Median SNCV

Ten studies provided median SNCV data of patients with DPN. The analysis revealed a significant improvement in median SNCV in combined-treatment patients compared to epalrestat-treated patients in two different treatment strategies (ALA 600 mg/d qd combined with epalrestat 50 mg tid: for 14 days – WMD: 7.12, 95% CI: 5.13–9.11, $P<0.00001$; for 21 days – WMD: 3.88, 95% CI: 3.08–4.68, $P<0.00001$; for 28 days – WMD: 9.97, 95% CI: 1.56–18.38, $P=0.02$. ALA 300 mg/d qd combined with epalrestat 50 mg tid for 28 days – pooled WMD 6.70, 95% CI: 5.75–7.65, $P<0.00001$; Table 2). There were significant differences

Table 2 Meta-analysis of ALA combined with epalrestat vs epalrestat monotherapy

Treatment strategy	Follow-up time (days)	Studies numbers	Number EG/CG	Heterogeneity		Model	WMD (95% CI)	*Z*	*P*-value	Difference between groups	
				I^2 (%)	*P*-value					χ^2	*P*-value
Median MNCV											
ALA 600 mg/d qd combined with epalrestat 50 mg tid	14	2[32,37]	70/70	0	0.97	Fixed	7.98 (6.17, 9.80)	8.63	0.00001	24.41	0.00001
	21	3[34,39,42]	95/95	70	0.03	Random	2.74 (1.50, 3.98)	4.33	0.0001		
	28	3[33,35,36]	92/92	98	0.00001	Random	9.01 (3.46, 14.56)	3.18	0.001		
ALA 300 mg/d qd combined with epalrestat 50 mg tid	28	2[31,38]	90/90	0	0.79	Fixed	6.12 (5.04, 7.20)	11.12	0.00001	NA	NA
Peroneal MNCV											
ALA 600 mg/d qd combined with epalrestat 50 mg tid	14	2[32,37]	70/70	0	0.62	Fixed	9.77 (7.78, 11.75)	9.64	0.00001	10.84	0.004
	21	4[34,39,41,42]	124/124	93	0.00001	Random	4.18 (1.49, 6.88)	3.05	0.002		
	28	3[33,35,36]	92/92	96	0.00001	Random	7.13 (3.94, 10.32)	4.38	0.0001		
ALA 300 mg/d qd combined with epalrestat 50 mg tid	28	2[31,38]	90/90	0	0.74	Fixed	6.68 (5.82, 7.55)	15.16	0.00001	NA	NA
Median SNCV											
ALA 600 mg/d qd combined with epalrestat 50 mg tid	14	2[32,37]	70/70	0	0.79	Fixed	7.12 (5.13, 9.11)	7.02	0.00001	10.51	0.005
	21	3[34,39,42]	95/95	0	0.77	Fixed	3.88 (3.08, 4.68)	9.54	0.00001		
	28	3[33,35,36]	92/92	99	0.00001	Random	9.97 (1.56, 18.38)	2.23	0.02		
ALA 300 mg/d qd combined with epalrestat 50 mg tid	28	2[31,38]	90/90	0	1.00	Fixed	6.70 (5.75, 7.65)	13.88	0.00001	NA	NA
Peroneal SNCV											
ALA 600 mg/d qd combined with epalrestat 50 mg tid	14	2[32,37]	70/70	0	0.61	Fixed	7.76 (5.77, 9.76)	7.62	0.00001	6.34	0.04
	21	4[34,39,41,42]	124/124	90	0.00001	Random	3.30 (0.45, 6.14)	2.27	0.02		
	28	3[33,35,36]	92/92	97	0.00001	Random	6.29 (3.01, 9.58)	3.76	0.0002		
ALA 300 mg/d qd combined with epalrestat 50 mg tid	28	2[31,38]	90/90	0	0.75	Fixed	4.27 (3.34, 5.20)	8.97	0.00001	NA	NA
TCSS											
ALA 600 mg/d qd combined with epalrestat 50 mg tid	21	3[34,39,41]	94/94	80	0.006	Random	−1.60 (−2.91, −0.29)	2.39	0.02	NA	NA
TSS											
ALA 600 mg/d qd combined with epalrestat 50 mg tid	21	3[34,39,41]	94/94	0	0.69	Fixed	−0.93 (−1.27, −0.60)	5.43	0.00001	NA	NA

Abbreviations: EG (experimental group), the group administered lipoic acid combined with epalrestat; CG (control group), the group administered lipoic acid monotherapy; ALA, α-lipoic acid; WMD, weighted mean difference; MNCV, median motor nerve conduction velocity; SNCV, median sensory nerve conduction velocity; NA, not available; TCSS, Toronto Clinical Scoring System; TSS, Total Symptom Score.

between the results obtained using ALA 600 mg/d qd combined with epalrestat 50 mg tid for different periods of time (χ^2=10.51, *P*=0.005).

Peroneal SNCV

Eleven trials were included for a comparison of peroneal SNCV results. The pooled results indicated that ALA combined with epalrestat significantly improved peroneal SNCV in different treatment strategies (ALA 600 mg/d qd combined with epalrestat 50 mg tid: for 14 days – WMD: 7.76, 95% CI: 5.77–9.76, *P*<0.00001; for 21 days – WMD: 3.30, 95% CI: 0.45–6.14, *P*=0.02; for 28 days – WMD: 6.29, 95% CI: 3.01–9.58, *P*=0.0002. ALA 300 mg/d qd combined with epalrestat 50 mg tid for 28 days – WMD: 4.27, 95% CI: 3.34–5.20, *P*<0.00001; Table 2). There were significant differences between the results obtained using ALA 600 mg/d qd combined with epalrestat 50 mg tid for different periods of time (χ^2=6.34, *P*=0.04).

TCSS

Three trials of 188 patients were included in the TCSS data. A random-effects model was developed because of the high

Table 3 Sensitivity analysis of median MNCV and SNCV

Treatment strategy	Follow-up time (days)	Eliminate study	Studies numbers	Numbers EG/CG	Heterogeneity		Model	WMD (95% CI)	*Z*	*P*-value
					I^2 (%)	*P*-value				
Median MNCV										
ALA 600 mg/d qd combined with epalrestat 50 mg tid	28	Liu[33]	2[35,36]	68/68	17	0.27	Fixed	6.64 (5.52, 7.36)	13.74	0.00001
Median SNCV										
ALA 600 mg/d qd combined with epalrestat 50 mg tid	28	Liu[33]	2[35,36]	68/68	34	0.22	Fixed	5.72 (4.98, 6.47)	15.06	0.00001

Abbreviations: EG (experimental group), the group administered lipoic acid combined with epalrestat; CG (control group), the group administered lipoic acid monotherapy; ALA, α-lipoic acid; WMD, weighted mean difference; MNCV, median motor nerve conduction velocity; SNCV, median sensory nerve conduction velocity.

heterogeneity (I^2=80%, P=0.006). The combined WMD was −1.60 (95% CI: −2.91, −0.29; P=0.02), revealing that the TCSS was significantly lower in the group receiving a combination of ALA 600 mg/d qd and epalrestat 50 mg tid than in the group receiving epalrestat monotherapy after 21 days of treatment (Table 2).

TSS

A fixed-effects model was created because no heterogeneity was found between the three studies (I^2=0%, P=0.69). The pooled data demonstrated that TSS was significantly lower in the combination treatment group (ALA 600 mg/d qd and epalrestat 50 mg tid) than in the epalrestat-alone group after 21 days of treatment (WMD: −0.93, 95% CI: −1.27, −0.60, $P<0.00001$; Table 2).

Adverse reactions

Only Han's study[38] reported an allergic reaction (1/55) in the combined-treatment group. Three trials[31,35,40] reported no adverse reactions in either the combination treatment or epalrestat group.

Sensitivity analysis

In the sensitivity analysis, the pooled data of the above outcomes did not show significant changes, indicating that the pooled results were steady. With respect to the ALA 600 mg qd combined with epalrestat 50 mg tid for the 28-day subgroup, the observed heterogeneity between therapies for the median MNCV and SNCV was absent after removing the study by Liu[33] (I^2=17%, P=0.27; I^2=34%, P=0.22). In this scenario, based on the results of a fixed-effects model, the combined-treatment regimen dramatically improved the median MNCV and SNCV compared to epalrestat alone (median MNCV: WMD: 6.64, 95% CI: 5.52, 7.36, $P<0.00001$; median SNCV: WMD: 5.72, 95% CI: 4.98, 6.47, $P<0.00001$; Table 3).

Publication bias

The funnel plot was essentially symmetrical, indicating no obvious publication bias in the total effectiveness rate. The Begg's test score was Z=1.11 (P=0.266), and the Egger's test score was t=1.31 (P=0.238), suggesting no evidence of publication bias (Figure 4).

Discussion

DN includes disorders of peripheral nerves and is a diabetic microvascular complication.[6] The prevalence of DPN in patients is approximately 30%, but up to 50% of these patients develop neuropathy during the course of the disease.[43] The total annual economic burden associated with DPN and its complications is estimated to be $4.6–13.7 billion (US), with approximately 27% of the direct medical expense of DM being attributed to DPN.[44] The pathogenesis of DPN is not clear; however, defects in metabolic and vascular pathways combined with oxidative stress play important roles in the onset and progression of nerve injury.[45] Many potential treatments, such as the curcumin derivative J147 and the methanolic extract of *Juglans regia L*. leaf, are effective in animal models of DPN; however, these treatments have not been validated in clinical trials.[46,47] ALA and epalrestat are efficacious in DPN patients and are popular in clinical use.[48,49] Many RCTs, especially in recent years, have confirmed that a combination of ALA and epalrestat improves MNCV and SNCV in DPN patients more efficiently than monotherapies.[29,33]

In our meta-analysis, 12 studies met our inclusion criteria. The data suggested that combination therapy was superior to epalrestat alone in improving the total effectiveness rate. Furthermore, the combination of ALA plus epalrestat increased the MNCV and SNCV of the median nerve and the nervus peroneus communis compared to epalrestat monotherapy. Notably, combination therapy was better in reducing the TCSS and TSS of patients with DPN. The results of the present meta-analysis are partially consistent with

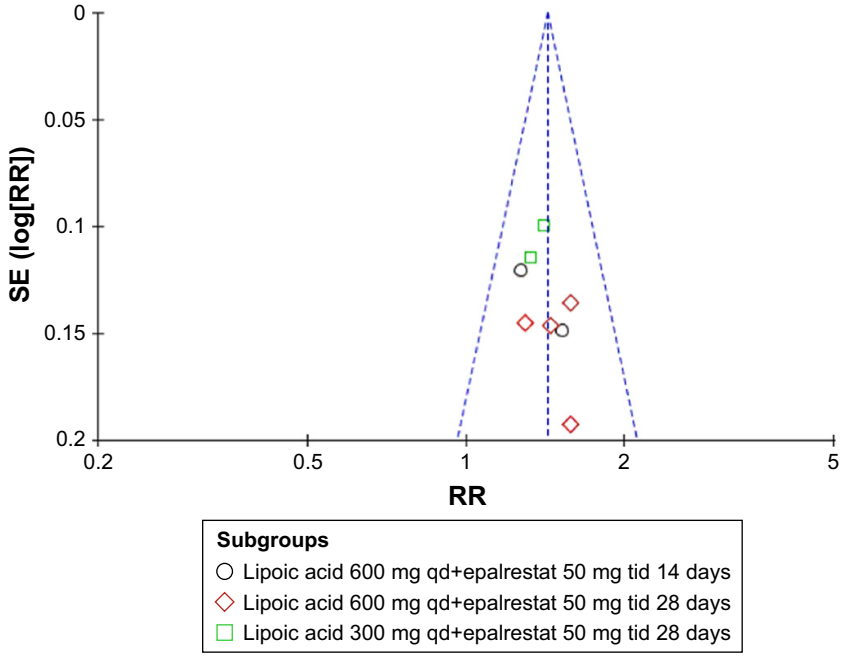

Figure 4 Funnel plot of total effectiveness rate.

another recent meta-analysis published in September 2015,[50] which demonstrated that ALA significantly improved the remission rate of clinical symptoms and nerve conduction velocity. However, combination therapy was not considered in this previous meta-analysis.[50] In addition, the Cochrane methodological criteria were not adequately fulfilled, and studies with different intervention times were not included, resulting in lower quality results.[50] More clinical trials were published in different databases in recent years, providing us with an opportunity to conduct a higher quality meta-analysis involving trials that considered different ALA doses and durations of intervention.

ALA directly eliminates free radicals, inhibits peroxidation, enhances blood flow, increases nerve Na^+ –K^+ ATPase activity, protects endothelial function, and increases the speed of nerve conduction.[14,45,51,52] Moreover, these data indicate that ALA benefits the vascular abnormalities of DPN and remarkably improves peripheral nerve function. In addition, ALA increases insulin sensitivity.[53] Therefore, ALA is a good option as a treatment for DPN that targets the pathogenic origins of the condition. Epalrestat prevents peripheral nerve injury by reducing expression of antioxidant enzyme and aldose reductase, relieving oxidative stress, and suppressing the overactive polyol pathway.[17] Epalrestat is, therefore, a valid choice for DPN treatment. The combination of ALA with epalrestat further improved the symptoms of DPN, NCV, and the peripheral blood levels of high sensitivity C-reactive protein.[54] The hospitalization cost study in 58 patients revealed that epalrestat was more economical than other drugs, such as alprostadil, and no difference in the total effectiveness rate was observed for the treatment of DPN for 1 month.[55] These data provide a promising option for DPN patients, especially those who have a poor clinical response to epalrestat monotherapy.

Limitations

There are some limitations of the present meta-analysis. First, most of the included clinical trials in this review were conducted in China, given that few combined-treatment regimens were undertaken outside of China. Data from other countries were not retrieved because of language and database limitations. Treatment strategies that were not repeated were also eliminated, which may have excluded some reliable treatment options. In addition, there were no placebo groups in any of the included trials, making it impossible to eliminate the possibility that the observed responses were due to the placebo effect.

Second, heterogeneity among clinical trials was observed in the analyses of the MNCV and SNCV of the median nerve, specifically for the treatment strategy consisting of ALA 600 mg qd combined with epalrestat 50 mg tid for 28 days. The sensitivity analysis of the pooled data demonstrated that the median MNCV and SNCV were not significantly altered with or without the inclusion of Liu's study,[33] indicating that the pooled results were steady. However, a contribution of Liu's study[33] to heterogeneity was identified, demonstrating

that different doses of ALA and different intervention times may be the sources of heterogeneity.

Third, most of the included clinical trials had relatively poor methodological quality. Fang[32] and Huang[41] did not mention details on randomization and reported no differences in age, gender, course of the disease, or fasting blood glucose between the two groups. Data from Deng's study[36] were inconsistent in terms of wording and should have been proofread by the author. We attempted to contact other authors via email or telephone for more detailed information regarding each trial, but little useful information was received. Considering the limitations of this review, CONSORT statements[56] are recommended for the reporting of future clinical trials.

Conclusion

Evidence from this analysis suggests that ALA combined with epalrestat is an efficient therapeutic option for patients with DPN. Future large-sample RCTs should be conducted to verify this finding.

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Author contributions

Ren Zhang and Xiaotong Wang conceived and designed the experiments. Haixiong Lin and Xiaotong Wang extracted the data, conducted statistical analysis, and wrote the manuscript. Shuai Xu checked the data. Yuanlin Jin and Ren Zhang interpreted the results. Ren Zhang supervised the manuscript writing. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Represents the search strategy for PubMed, CNKI

Number	Search terms
Search strategy used in PubMed	
#1	thioctic [All Fields]
#2	acid [All Fields]
#3	#1 and #2
#4	lipoic [All Fields]
#5	acid [All Fields]
#6	#4 and #5
#7	Alpha lipoic acid [MeSH]
#8	Alpha lipoic acid [TIAB]
#9	Alpha lipoic acid [All Fields]
#10	lipoic acid [MeSH]
#11	lipoic acid [TIAB]
#12	lipoic acid [All Fields]
#13	thioctic acid [MeSH]
#14	thioctic acid [TIAB]
#15	thioctic acid [All Fields]
#16	#3 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17	diabetic [All Fields]
#18	peripheral neuropathy [All Fields]
#19	#17 and #18
#20	neuropathy [All Fields]
#21	#17 and #20
#22	diabetic neuropathy [All Fields]
#23	diabetic peripheral neuropathy [All Fields]
#24	diabetic neuropathy [MeSH]
#25	diabetic peripheral neuropathy [MeSH]
#26	diabetic neuropathy [TIAB]
#27	diabetic peripheral neuropathy [TIAB]
#28	#19 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#29	epalrestat [MeSH]
#30	epalrestat [Supplementary Concept]
#31	epalrestat [All Fields]
#32	epalrestat [TIAB]
#33	#29 or #30 or #31 or #32
#34	randomized [MeSH]
#35	randomized controlled trial [MeSH]
#36	randomized controlled trial [All Fields]
#37	randomisation [MeSH]
#38	#34 or #35 or #36 or #37
#39	blind [MeSH]
#40	#16 and #28 and #33 and #38 and #39
Search strategy used in CNKI	
#1	diabetes mellitus [MeSH]
#2	peripheral neuropathy [MeSH]
#3	#1 and #2
#4	diabetes mellitus [Full text]
#5	peripheral neuropathy [Full text]
#6	#4 and #5
#7	diabetes mellitus [key word]
#8	peripheral neuropathy [key word]
#9	#7 and #8
#10	diabetic peripheral neuropathy [MeSH]
#11	diabetic peripheral neuropathy [key word]
#12	diabetic peripheral neuropathy [Full text]
#13	#3 or #6 or #9 or #10 or #11 or #12
#14	lipoic acid [MeSH]
#15	lipoic acid [key word]
#16	lipoic acid [Full text]
#17	lipoic acid capsule [Full text]
#18	lipoic acid injection [Full text]
#19	#14 or #15 or #16 or #17 or #18
#20	epalrestat [MeSH]
#21	epalrestat [key word]
#22	epalrestat [Full text]
#23	#20 or #21 or #22
#24	#13 and #19 and #23

Abbreviation: CNKI, China National Knowledge Infrastructure.

Table S2 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1–2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1–2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2–3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2–3
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3–4
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4–5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group; 2) effect estimates and confidence intervals, ideally with a forest plot.	4–8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4–8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	4
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	8–9
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	9–10
Conclusion	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	10

Notes: From: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.