INPLASY PROTOCOL

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Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None.

Efficacy and acceptability of ALC for diabetic peripheral neuropathy in adults: a network meta-analysis

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Review question / Objective: **To evaluate the comparative effects of acetyl-Levo-carnitine Hydrochloride (ALC) versus other commonly used oral monotherapies, including epalrestat, mecobalamine, a-lipoic acid, and pancreatic kininogenase on nerve conduction velocities, clinical symptom and sign scores in adults with diabetic peripheral neuropathy (DPN).**
Condition being studied: **Adults with diabetic peripheral neuropathy.**
Information sources: **We will search the English electronic databases (including MEDLINE/PubMed, Embase, the Cochrane Library, and Web of Science), and the Chinese biomedical databases (including CBM, CNKI, Wanfang, and VIP) in February 2020, with no date/time, language, and document type limitations.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 July 2020 and was last updated on 29 July 2020 (registration number INPLASY202070126).

INTRODUCTION

Review question / Objective: **To evaluate the comparative effects of acetyl-Levo-carnitine Hydrochloride (ALC) versus other commonly used oral monotherapies, including epalrestat, mecobalamine, a-lipoic acid, and pancreatic kininogenase on nerve conduction velocities, clinical symptom and sign scores in adults with diabetic peripheral neuropathy (DPN).**

Condition being studied: **Adults with diabetic peripheral neuropathy.**

METHODS

Participant or population: Patients aged 18 years or older, of both sexes, with a primary diagnosis of diabetic peripheral neuropathy (according to any standard criteria) will be included.

Intervention: Acetyl-Levo-carnitine Hydrochloride (ALC).

Comparator: Epalrestat, methylcobalamin, a-lipoic acid, pancreatic kininogenase. The synthesis comparator set consists of all the interventions listed above and placebo. If we identify in the included studies interventions that we are not aware of, we will consider them as eligible and we will include them in the network after assessing their comparability with those named above.

Study designs to be included: All RCTs comparing one active drug with another or with placebo in the treatment of DPN will be included. Only monotherapy studies will be included.

Eligibility criteria: Inclusion criteria: any RCT comparing ALC with other monotherapy for DPN. Exclusion criteria: 1) study design is not RCT; 2) population is not exclusively the patients with DPN or an analyzed subgroup of them; 3) Two compared groups including non-pharmacy treatment, Chinese medicinal treatment, or combination of Chinese traditional and western medicine; 4) language is not in English or Chinese; 5) No abstract or unclear abstract but given the title, aims, or objectives is unlikely to be a relevant record.

Information sources: We will search the English electronic databases (including MEDLINE/PubMed, Embase, the Cochrane Library, and Web of Science), and the Chinese biomedical databases (including CBM, CNKI, Wanfang, and VIP) in February 2020, with no date/time, language, and document type limitations.

Main outcome(s): Nerve conduction velocity (NCV). We will collect the outcome data measured at the longest follow-up unless otherwise specified.

Additional outcome(s): 1. Pain 2. Neurological symptoms and signs 3. Vibration perception threshold 4. Adverse events We will collect the outcome data measured at the longest follow-up unless otherwise specified.

Data management: Two review authors extracted the data independently according to a standard extraction form with respect to trial information, population and treatment characteristics, reported outcome data, and information on methodology. Any disagreements will be resolved by discussion, with the assistance from a third party if necessary.

Quality assessment / Risk of bias analysis: Two review authors assessed the quality of included studies independently. If any disagreement, a consensus through discussion was reached. We evaluated every domain of risk of bias, on the basis of the standard criteria outlined by the Cochrane Collaboration (Higgins 2011), including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Disagreements were resolved by discussion, with the assistance from a third party if necessary.

Strategy of data synthesis: A random-effects network meta-analysis within a Bayesian framework was performed. MD for each outcome with 95% CI was summarized. We estimated the ranking probabilities for all treatments of being at each possible rank for each intervention. The treatment hierarchy was summarized and reported as surface under the cumulative ranking curve (SUCRA) and mean ranks, which was considered as secondary endpoint. SUCRA is a percentage interpreted as the probability of a treatment is the most effective without uncertainty on the outcome, which is equal to 1 when the treatment is certain to be the best and 0 when it is certain to be the

worst. All analyses were conducted using R 3.6.2 (gemtc package). If meta-analysis is considered inappropriate, we will describe the outcome data separately.

Subgroup analysis: None.

Sensibility analysis: None.

Language: Without language limitation on the search. Records with language other in English or Chinese will be excluded when screening.

Country(ies) involved: China.

Keywords: Diabetic peripheral neuropathy; acetyl-levo-carnitine; network meta-analysis.

Contributions of each author:
Author 1 - Qi Pan - Qi Pan designed the experiment, drafted the manuscript and reviewed the manuscript.
Author 2 - Xiaofan Jia - Xiaofan Jia designed the experiment and analyzed the data.
Author 3 - Xiaoxia Wang - Xiaoxia Wang performed the experiment and drafted the manuscript.
Author 4 - Lina Zhang - Lina Zhang performed the experiment.
Author 5 - Fuli Man - Fuli Man performed the experiment.
Author 6 - Weihao Wang - Weihao Wang analyzed the data.
Author 7 - Mengmeng li - Mengmeng Li performed the experiment.
Author 8 - Lixin Guo - Lixin Guo designed the experiment and reviewed the manuscript.