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L-ornithine L-aspartate for people with cirrhosis and hepatic encephalopathy (Protocol)

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[Intervention Protocol]

L-ornithine L-aspartate for people with cirrhosis and hepatic encephalopathy

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the beneficial and harmful effects of L-ornithine L-aspartate versus placebo, no intervention, or other active interventions for people with cirrhosis and hepatic encephalopathy.

BACKGROUND

Hepatic encephalopathy is a neuropsychiatric complication associated with liver insufficiency or portal-systemic shunting (EASL/AASLD 2014a; EASL/AASLD 2014b). Hepatic encephalopathy occurs during the decompensated stage of cirrhosis. The severity of the impairment ranges from minor signs to overt coma and the degree of the neuropsychiatric changes increases with the severity of the underlying liver disease (Bajaj 2009). Previous studies have found that more than 50% of people with cirrhosis have minimal hepatic encephalopathy (Lauridsen 2011). Approximately 20% of people with decompensated cirrhosis have overt hepatic encephalopathy at least once during their clinical course (D'Amico 1986; de Jongh 1992; Zipprich 2012). Both overt and minimal hepatic encephalopathy are associated with impairment in the performance of complex tasks, such as driving (Schomerus 1981; Bajaj 2009; Kircheis 2009), and they have a detrimental effect on quality of life (Groeneweg 1998). The cumulative incidence of overt hepatic encephalopathy is as high as 40% and is an independent predictor of increased mortality (Bustamante 1999; del Olmo 2000; D'Amico 2006; Spadaro 2007; Stewart 2007; Bajaj 2011). The survival probability in people with cirrhosis after their first episode of hepatic encephalopathy is about 42% at one year and 23% at three years (Bustamante 1999).

Description of the condition

Minimal hepatic encephalopathy describes people with cirrhosis with no clinically apparent signs or symptoms, but with abnormalities in neuropsychometric or neurophysiological performance (Ferenci 2002; Guerit 2009; Atluri 2011). Overt (clinically apparent) hepatic encephalopathy manifests as a neuropsychiatric syndrome encompassing a wide spectrum of mental and motor dis-

orders (Weissenborn 1998; Ferenci 2002). It may develop over a period of hours or days without an identifiable reason, or be associated with precipitating events such as gastrointestinal bleeding, infection, or alcohol misuse. People may return to normal or may have some degree of impairment between episodes (Bajaj 2010). Less frequently, people have stable, persistent neuropsychiatric abnormalities often due to extensive spontaneous or surgical portal-systemic shunting. The changes in mental state range from subtle alterations in personality, intellectual capacity, and cognitive function to deep coma. The changes in motor function may include rigidity, disorders of speech production, tremor, delayed diadochocinetic movements, hyper- or hypo-reflexia, choreoathetoid movements, Babinsky's sign, and transient focal symptoms (Victor 1965; Weissenborn 1998; Cadranel 2001). Asterixis, also known as*a* flapping tremor, is the best known motor abnormality. Individuals with overt hepatic encephalopathy also show other abnormalities such as impaired psychomotor performance (Schomerus 1998), neurophysiological function (Parsons-Smith 1957; Chu 1997), and alterations in cerebral neurochemical/neurotransmitter homeostasis (Taylor-Robinson 1994), blood flow and metabolism (O'Carroll 1991), and fluid homeostasis (Haussinger 2000). There is no gold standard for the diagnosis of this hepatic encephalopathy, but a number of individual techniques exist, which can be used alone or in combination (Ferenci 2002; Kircheis 2002; Montagnese 2004; Bajaj 2008; Randolph 2009). Clinicians as well as researchers generally use the West Haven Criteria to assess changes in the mental state (Conn 1977) and the Glasgow Coma Score to assess the consciousness level (Teasdale 1974). A number of paper and pencil psychometric tests are used in the evaluation of cognitive function. The Psychometric Hepatic Encephalopathy Score, which comprises five paper and pencil tests to assess attention, visual perception, and visuo-constructive abilities, is the most widely used psychometric test (Schomerus 1998; Weissenborn 2001).

The jointly published guidelines from the European and American Associations for the Study of Liver diseases (EASL/AASLD 2014a; EASL/AASLD 2014b) recommend that hepatic encephalopathy should be classified based on the underlying disease, the severity of manifestations, the time course, and the existence of precipitating factors. Hepatic encephalopathy is classed as type A when associated with acute liver failure, type B when resulting from porto-systemic bypass or shunting, or type C when associated with cirrhosis. The hepatic encephalopathy continuum is subdivided into episodic, which refers to an acute episode of hepatic encephalopathy (previously known as acute). Recurrent hepatic encephalopathy refers to bouts of hepatic encephalopathy occurring with a time interval of six months or less. Persistent hepatic encephalopathy refers to people with a pattern of behavioral alterations that are always present and interspersed with relapses of overt hepatic encephalopathy. Previous trials classed recurrent and persistent hepatic encephalopathy as chronic, chronic persistent, or chronic intermittent hepatic encephalopathy (Stauch 1998). Depending on the existence of precipitating factors, hepatic encephalopathy is defined as non-precipitated or precipitated (EASL/AASLD 2014a; EASL/AASLD 2014b).

Description of the intervention

L-ornithine L-aspartate is a stable salt of the amino acids ornithine and aspartic acid, which is administered orally or intravenously (Rose 1998; Blanco Vela 2011a). The dose and treatment duration depends on the mode of administration. Previous trials comparing oral L-ornithine L-aspartate versus lactulose used a dose of nine grams of L-ornithine-L-aspartate per day (Poo 2006; Poo 2007) or up to 15 to 18 grams per day (Stauch 1998; Fleig 1999; Rees 2000; Mittal 2009; Abdo-Francis 2010; Alvares-da-Silva 2011; Mittal 2011; Ndraha 2011; Alvares-da-Silva 2014; Sharma 2014). Trials assessing intravenous L-ornithine L-aspartate for the treatment of hepatic encephalopathy in participants with cirrhosis used a total dose of 20 grams per day for three to eight consecutive days (Kircheis 1997; Abid 2005; Ahmad 2008; Lim 2010; Schmid 2010; Abid 2011; Hasan 2012; Sharma 2012; Sharma 2014), but up to 30 grams per day in participants with transjugular intrahepatic porto-systemic shunts (Bai 2013a; Bai 2014).

How the intervention might work

Ammonia plays a key role in the pathogenesis of hepatic encephalopathy (Butterworth 2014). Nitrogenous products in the diet, bacterial metabolism of urea and proteins in the colon, and deamination of glutamine in the small intestine are the main sources of ammonia. L-ornithine L-aspartate has ammonia-lowering properties, which are affected via stimulation of the urea cycle in the liver and stimulation of the production of glutamine in the periphery (Rose 1999). In the liver, ornithine stimulates the activity of carbamoyl phosphate synthetase while the aspartate moiety stimulates the activity of arginase through nitrogen donation. Ammonia is then detoxified into urea (Gebhardt 1997; Rose 1998, Blanco Vela 2011b). L-ornithine L-aspartate also enhances the activities of ornithine and aspartate transaminases in peripheral tissues to promote the production of glutamate, which predominantly occurs in muscle. The enzyme glutamine synthetase subsequently converts glutamate to glutamine (Gebhardt 1997).

Why it is important to do this review

Randomised clinical trials (RCTs) in participants with cirrhosis have reached different conclusions regarding the effect of L-ornithine L-aspartate on hepatic encephalopathy for people with cirrhosis (Kircheis 1997; Stauch 1998; Poo 2006; Ahmad 2008; Schmid 2010; Abid 2011; Mittal 2011; Ndraha 2011; Alvares-da-Silva 2014; Bai 2014; Sharma 2014). Some trials found beneficial effects in minimal and overt hepatic encephalopathy

when used alone (Kircheis 1997; Stauch 1998; Ahmad 2008; Sharma 2014) or combined with branched-chain amino acids (Ndraha 2011). Other trials found no convincing effects of L-ornithine L-aspartate on hepatic encephalopathy (Schmid 2008; Schmid 2010; Abid 2011; Alvares-da-Silva 2014).

Four meta-analyses have evaluated the effects of L-ornithine L-aspartate for hepatic encephalopathy (Jiang 2009; Soarez 2009; Perez Hernandez 2011; Bai 2013b). A meta-analysis published in 2009 included three RCTs with a total of 212 participants (Kircheis 1997; Stauch 1998; Poo 2006) and found that L-ornithine L-aspartate was associated with a beneficial effect on overt, but not minimal hepatic encephalopathy compared with placebo or lactulose (Jiang 2009). A meta-analysis of four placebo-controlled trials with 217 participants (Staedt 1993; Kircheis 1997; Stauch 1998; Rees 2000) found that although L-ornithine L-aspartate reduced blood ammonia levels it had no effect on hepatic encephalopathy per se (Soarez 2009). A subsequent meta-analysis from 2011 (Perez Hernandez 2011) including five RCTs involving 422 participants with cirrhosis (Staedt 1993; Kircheis 1997; Kircheis 2002; Ahmad 2008; Abdo-Francis 2010) and 1 RCT including 201 participants with fulminant liver failure (Acharya 2009) found that L-ornithine L-aspartate improved neuropsychiatric assessments and decreased venous blood ammonia concentrations. A meta-analysis from 2013 (Bai 2013b) evaluated eight trials with 646 participants (Kircheis 1997; Stauch 1998; Poo 2006; Ahmad 2008; Schmid 2010; Abid 2011; Mittal 2011; Ndraha 2011) and found that L-ornithine L-aspartate was associated with beneficial effects in overt and minimal hepatic encephalopathy and on fasting ammonia compared with placebo, no intervention, or lactulose. The meta-analyses from 2011 and 2013 did not adjust the quantitative result based on the quality of the evidence and did not include data from unpublished trials.

We plan to conduct an updated systematic review with meta-analyses of published and unpublished RCTs of L-ornithine L-aspartate for hepatic encephalopathy in people with cirrhosis, following recommendations for best practice. Currently, there is no universally-accepted treatment for hepatic encephalopathy. The advantage of L-ornithine L-aspartate, should it prove efficacious and safe, is that it is available not only as an oral preparation but also as an intravenous infusion; as such it may also be of benefit to people with acute hepatic encephalopathy which is particularly difficult to treat.

OBJECTIVES

To assess the beneficial and harmful effects of L-ornithine L-aspartate versus placebo, no intervention, or other active interventions for people with cirrhosis and hepatic encephalopathy.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials (RCTs) regardless of their publication status, language, or blinding in our primary analyses. If, during the selection of trials, we identify observational studies (i.e. quasi-randomised studies; cohort studies; or patient reports) that report adverse events caused by or associated with the interventions in our review, we will include these studies for a review of the adverse events. We will not specifically search for observational studies for inclusion in this review, which is a known limitation of our systematic review.

Types of participants

We will include participants with cirrhosis who have overt or minimal hepatic encephalopathy or who are at risk of developing hepatic encephalopathy. We will include participants in our primary analyses regardless of sex, age, aetiology of the underlying liver disease or precipitating factors. We will exclude data on people with acute liver failure.

Types of interventions

We will compare: i) L-ornithine L-aspartate versus placebo or no intervention; and ii) L-ornithine L-aspartate versus nonabsorbable disaccharides, antibiotics, probiotics, or branched-chain amino acids. We will include trials irrespective of the doses, treatment durations, or mode of administration. We will allow co-interventions administered equally to allocation arms.

We do not plan to include analyses of glycerol phenylbutyrate, ornithine phenylacetate, or spherical carbon adsorbents (AST-120), which will be evaluated in a separate review (Morgan 2016).

Types of outcome measures

We will assess all outcomes at the maximum duration of follow-up (Gluud 2016).

Primary outcomes

1. Mortality (all-cause).
2. Hepatic encephalopathy. We will assess the outcome using the primary investigators' overall assessment of: i) number of participants who developed hepatic encephalopathy; and ii) number of participants without a clinically-relevant improvement in hepatic encephalopathy.
3. Serious adverse events: defined as any untoward medical occurrence that led to death, was life threatening or required hospitalisation or prolongation of hospitalisation (ICH-GCP 1997). We will analyse serious adverse events as a composite outcome (Gluud 2016).

Secondary outcomes

1. Quality of life.
2. Non-serious adverse events (all adverse events that do no fulfil the criteria listed under serious adverse events).
3. Liver-related mortality.

Exploratory outcomes

1. Number Connection Test.
2. Portal Hepatic Encephalopathy Score.
3. Blood ammonia concentrations.
4. Electroencephalography.

Search methods for identification of studies

Electronic searches

We will search Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2016), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (Ovid SP), Embase (Ovid SP), and Science Citation Index Expanded (Web of Science) (Royle 2003). We present preliminary search strategies with the expected time spans of the searches in Appendix 1.

Searching other resources

We will scan reference lists of relevant articles, and proceedings from meetings of the British Society for Gastroenterology (BSG), the British Association for the Study of the Liver (BASL), the European Association for the Study of the Liver (EASL), the United European Gastroenterology Week (UEGW), the American Gastroenterological Association (AGA), the American Association for the Study of Liver Diseases (AASLD), and the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN). We will write to the principal authors of trials and the pharmaceutical companies involved in the production of L-ornithine L-aspartate for additional information about completed trials and for information about any ongoing trials.

We will also search online trial registries such as ClinicalTrial.gov (clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trial Registry Platform (www.who.int/ictrp), and the Food and Drug Administration (FDA) (www.fda.gov), as well as pharmaceutical company sources for ongoing or unpublished trials. We will use the same or similar search terms as will be used for searching the electronic databases (Appendix 1).

Data collection and analysis

Selection of studies

Two authors (Caroline Stokes and Ee Teng Goh) will read the electronic search output, perform additional manual searches, and list potentially eligible trials. All authors will read the potentially eligible trials and participate in the final selection of trials for inclusion. For trials described in more than one publication, we will select the paper with the longest duration of follow-up as our primary reference. We will describe the characteristics of included trials in summary tables, and excluded trials with the reason for exclusion. A third author (MM or LLG) will act as ombudsman in case of disagreements. We will resolve contrary opinions through discussion.

Data extraction and management

The collected data will include information on:

- trials: design (cross-over or parallel), settings (number of clinical sites; outpatient or inpatient; inclusion period), country of origin; publication status;
- participants: mean age, proportion of men, aetiology of cirrhosis, type of hepatic encephalopathy (diagnostic criteria and definitions/terminology); previous history of hepatic encephalopathy; and
- interventions: type, dose, duration of therapy, mode of administration. We will gather the primary and secondary outcome data, including the definitions used in the assessment of overall improvement of hepatic encephalopathy, and bias control.

We will request missing data and other information from authors of included trials.

Assessment of risk of bias in included studies

We will assess bias control using the domains described in the Cochrane Hepato-Biliary Group module (Gluud 2016), and classify the risk of bias for separate domains as high, unclear, or low (Higgins 2011).

Allocation sequence generation

- Low risk of bias: sequence generation achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, or throwing dice are adequate if performed by an independent person but not otherwise.
- Unclear risk of bias: not described.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: allocation by a central and independent randomisation unit, administration of coded, identical drug containers/vials or sequentially-numbered, opaque, sealed envelopes.
- Unclear risk of bias: not described.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and personnel using placebo, double dummy or similar. We will define lack of blinding as not likely to affect the assessment of mortality.
- Unclear risk of bias: not described.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding (non-mortality outcomes).

Blinding of outcome assessors

- Low risk of bias: blinding of the outcome assessor using a placebo, double dummy or similar. We will define lack of blinding as not likely to affect the assessment of mortality.
- Unclear risk of bias: there was insufficient information.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding (non-mortality outcomes).

Incomplete outcome data

- Low risk of bias: missing data unlikely to make treatment effects depart from plausible values. The investigators used sufficient methods, such as intention-to-treat analyses with multiple imputations or carry-forward analyses, to handle missing data.
- Unclear risk of bias: insufficient information.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported clinically-relevant outcomes (mortality, hepatic encephalopathy, and serious adverse events). If we had access to the original trial protocol, the outcomes selected were those called for in that protocol. If we obtained information from a trial registry (such as www.clinicaltrials.gov), we only used that information if the investigators registered the trial before inclusion of the first participant.
- Unclear risk of bias: not all predefined outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appears to be free of industry sponsorship or other type of for-profit support.
- Unclear risk of bias: insufficient information about support or sponsorship.
- High risk of bias: the trial received funding or other support from a pharmaceutical company.

Other bias

- Low risk of bias: the trial appeared to be free of other biases including: medicinal dosing problems or follow-up (as defined below).
- Unclear risk of bias: the trial may or may not have been free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias such as the administration of inappropriate treatments being given to the controls (e.g. an inappropriate dose) or follow-up (e.g. the trial included different follow-up schedules for participants in the allocation groups).

Overall bias assessment

- Low risk of bias: all domains were low risk of bias using the definitions described above.
- High risk of bias: one or more of the bias domains were of unclear or high risk of bias.

Measures of treatment effect

We will use risk ratios (RR) for dichotomous outcomes and the standardised mean differences (SMD) for continuous outcomes, both with 95% confidence intervals (CI). For our primary outcomes, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) based on the risk difference (RD) as 1/RD (Higgins 2011).

Unit of analysis issues

We will include data from the first treatment period of cross-over trials. We will include separate pair-wise comparisons from multi-arm trials. Accordingly, if a trial compares L-ornithine L-aspartate, rifaximin, and lactulose, we will conduct separate analyses of L-ornithine L-aspartate versus rifaximin and L-ornithine L-aspartate versus lactulose.

Dealing with missing data

We will extract data on all randomised participants in order to allow intention-to-treat analyses and conduct a worst-case scenario analysis using simple imputation (Higgins 2008). Our worst-case scenario analysis will include participants with missing outcome data in the intervention arm and those in the control arm as successes. We will also conduct an extreme worst-case scenario analysis in which missing outcome data are counted as failures in the experimental arm and successes in the control arm (Gluud 2016).

Assessment of heterogeneity

We will express heterogeneity as I^2 values using the following thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and > 80% (considerable), and include information in the 'Summary of findings' tables.

Assessment of reporting biases

For meta-analyses with at least 10 RCTs, we will assess reporting biases through regression analyses and funnel plots.

Data synthesis

We will perform the analyses in Review Manager 5 (RevMan 2014), STATA (Stata version 14), and Trial Sequential Analysis (TSA 2011).

Meta-analysis

In our primary analyses, we will stratify trials based on the type of control intervention (e.g. placebo or no intervention, nonabsorbable disaccharides, antibiotics, probiotics, and branched-chain amino acids). We plan to compare the fixed-effect and random-effects estimates of the intervention effect. If the estimates are similar, then we will assume that any small-study effects have little effect on the intervention effect estimate. If the random-effects estimate is more beneficial, we will re-evaluate whether it is reasonable to conclude that the intervention was more effective in the smaller studies. If the larger studies tend to be those conducted with greater methodological rigour, or conducted in circumstances more typical of the use of the intervention in practice, then we will report the results of meta-analyses restricted to the larger, more rigorous studies. Based on the expected clinical heterogeneity, we expect that a number of analyses will display statistical between-trial heterogeneity (I^2 > 0%). For random-effects models, precision will decrease with increasing heterogeneity and confidence intervals will widen correspondingly. We therefore expect that the random-effects model will give the most conservative (and a more correct) estimate of the intervention effect. Accordingly, we plan to report the results of our analyses based on random-effects meta-analyses.

Trial Sequential Analysis

We will perform Trial Sequential Analysis (Wetterslev 2008; TSA 2011) to evaluate the risk of type 1 and type 2 errors and to evaluate futility (Higgins 2008) in the analyses of our primary outcomes. We will define the required information size (also known as the 'heterogeneity adjusted required information size') as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and assumed control risk (ACR). We will define firm evidence as established if the Z-curve crosses the monitoring boundary (also known as the 'trial sequential monitoring boundary') before reaching the required information size. We will construct futility boundaries to evaluate the uncertainty of obtaining a chance neutral finding. We will perform the analyses with alpha set to 5%, power to 80%, and model-based diversity. We will conduct the analyses including all RCTs and including RCTs with a low risk of bias. Based on previous evidence (Kircheis 1997; Stauch 1998; Fleig 1999; Ahmad 2008; Mittal 2009; Schmid 2010; Abid 2011; Mittal 2011; Hasan 2012; Sharma 2014), we will set the RRR to 20% and the ACR to 15% in the analysis of mortality, the RRR to 30% and the ACR to 45% in the analysis of hepatic encephalopathy, and the RRR to 25% and ACR to 20% in the analysis of serious adverse events.

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses to investigate heterogeneity based on stratification of trials by risk of bias and the type of hepatic encephalopathy (overt, minimal, or prevention; acute or chronic (corresponding to episodic or recurrent); and primary or secondary prevention). We will also compare RCTs evaluating intravenous or oral L-ornithine L-aspartate.

Sensitivity analysis

We plan to perform sensitivity analyses excluding RCTs that include participants with iatrogenic shunts, and to conduct worst-case and extreme worst-case scenario analyses (as described above).

'Summary of findings' tables

We will use the GRADE system (Brozek 2008) to evaluate the quality of the evidence for outcomes reported in the review, considering the within-trial risk of bias, inconsistency, imprecision, indirectness, and publication bias. We will include the information in the interpretation of our results and report conclusions based on the 'EPICOT' principle (Brown 2006).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	(ornit* and aspart*) and hepatic encephalopath*
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 ornit* in All Text #2 MeSH descriptor Ornithine explode all trees #3 aspart* in All Text #4 MeSH descriptor Aspartic Acid explode all trees #5 (#1 or #2) and (#3 or #4) #6 cirrhosis in All Text #7 Encephalopath* in All Text #8 MeSH descriptor Hepatic Encephalopathy explode all trees #9 #6 or #7 or #8 #10 #5 and #9
MEDLINE (Ovid SP)	1946 to the date of search.	#1 Randomized controlled trial pt. #2 Controlled clinical trial.pt. #3 exp Randomized controlled trial/ #4 exp Random allocation/ #5 exp Double-blind method/ #6 exp Single-blind method/ #7 clinical trial.pt. #8 exp clinical trial/ #9 (clin$ adj25 trial$).ti,ab. #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #11 singl$ or doubl$ or tripl$ or trebl$).ti,ab. #12 (blind$ or mask$).ti,ab. #13 #11 and #12 #14 exp Placebos/ #15 placebo$.ti,ab. #16 random$.ti,ab. #17 #14 or #15 or #16 #18 #10 or #13 or #17 #19 animals/ not humans/ #20 #18 not #19 #21 exp Ornithine/ #22 exp Aspartic Acid/ #23 #21 and #22 #24 (ornit$ and aspart$).ti,ab. #25 #23 or #24 #26 exp Hepatic Encephalopathy/ #27 Encephalopathy.ti,ab. #28 cirrhosis.ti,ab. #29 #26 or #27 or #28 #30 #20 and #25 and #29

(*Continued*)

Embase (Ovid SP)	1974 to the date of search.	#1 Controlled study/ #2 Randomized Controlled trial/ #3 double blind procedure/ #4 single blind procedure/ #5 crossover procedure/ #6 drug comparison/ #7 placebo/ #8 random*.ti, ab. #9 crossover.ti,ab. #10 cross-over.ti, ab. #11placebo*.ti,ab. #12 ((doubl* or singl* or tripl* or trebl*) AND (blind* or mask*)).ti, ab. #13 (comparative AND trial*).ti,ab. #14 (clinical AND trial*).ti,ab. #15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 #16 nonhuman/ #17 animal/ not (human/ and animal/) #18 #16 or #17 #19 #15 not #18 #20 'aspartic acid'/ #21 'ornithine'/ #22 #20 and #21 #23 ornit*.ti, ab. #24 aspart*.ti, ab. #25 #23 and #24 #26 #22 or #25 #27 'hepatic encephalopathy'/ #28 encephalopath*.ti, ab. #29 #27 or #28 #30 #19 and #26 and #29
Science Citation Index Expanded (Web of Science)	1900 to the date of search.	#1 TS=(ornit* and aspart*) #2 TS=(hepatic encephalopath*) #3 #1 and #2 #4 TS=(random* OR blind* OR placebo* OR meta-analys* OR systematic review*) #5 #3 and #4

CONTRIBUTIONS OF AUTHORS

Lise L Gluud prepared a draft for this protocol. All review authors participated in the critical revision of the protocol and have approved the final version.

DECLARATIONS OF INTEREST

Caroline S Stokes: nothing to declare.

Ee Teng Goh: nothing to declare.

Hendrik Vilstrup: nothing to declare.

Marsha Y Morgan: nothing to declare.

Lise L Gluud: Abbvie, Merck, Norgine (investigator in trials), Novo Nordisk (travel expenses), Norgine (teaching).

SOURCES OF SUPPORT

Internal sources

- none, Other.

External sources

- none, Other.

NOTES

This protocol replaces a previous protocol by Yuan W et al., with the title 'L-ornithine-L-aspartate for hepatic encephalopathy', that was abandoned in 2011 (Yuan 2008) and withdrawn from publication.