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Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis (Review)

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Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis

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A B S T R A C T

Background

Hepatic encephalopathy is a common complication of cirrhosis, with high related morbidity and mortality. Its presence is associated with a wide spectrum of change ranging from clinically obvious neuropsychiatric features, known as 'overt' hepatic encephalopathy, to abnormalities manifest only on psychometric or electrophysiological testing, 'minimal' hepatic encephalopathy. The exact pathogenesis of the syndrome is unknown but ammonia plays a key role. Drugs that specifically target ammonia include sodium benzoate, glycerol phenylbutyrate, ornithine phenylacetate, AST-120 (spherical carbon adsorbent), and polyethylene glycol.

Objectives

To evaluate the beneficial and harmful effects of pharmacotherapies that specifically target ammonia versus placebo, no intervention, or other active interventions, for the prevention and treatment of hepatic encephalopathy in people with cirrhosis.

Search methods

We searched the Cochrane Hepato-Biliary Controlled Trials Register, CENTRAL, MEDLINE, Embase, and three other databases to March 2019. We also searched online trials registries such as ClinicalTrials.gov, European Medicines Agency, WHO International Clinical Trial Registry Platform, and the Food and Drug Administration for ongoing or unpublished trials. In addition, we searched conference proceedings, checked bibliographies, and corresponded with investigators.

Selection criteria

We included randomised clinical trials comparing sodium benzoate, glycerol phenylbutyrate, ornithine phenylacetate, AST-120, and polyethylene glycol versus placebo or non-absorbable disaccharides, irrespective of blinding, language, or publication status. We included participants with minimal or overt hepatic encephalopathy or participants who were at risk of developing hepatic encephalopathy.

Data collection and analysis

Two review authors independently extracted data from the included reports. The primary outcomes were mortality, hepatic encephalopathy, and serious adverse events. We undertook meta-analyses and presented results using risk ratios (RR) or mean differences (MD), both with 95% confidence intervals (CIs), and I^2 statistic values as a marker of heterogeneity. We assessed bias control using the Cochrane Hepato-Biliary domains and the certainty of the evidence using GRADE.

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Main results

Eleven randomised clinical trials fulfilled our inclusion criteria. Two trials evaluated the prevention of hepatic encephalopathy while nine evaluated the treatment of hepatic encephalopathy. The trials assessed sodium benzoate (three trials), glycerol phenylbutyrate (one trial), ornithine phenylacetate (two trials), AST-120 (two trials), and polyethylene glycol (three trials). Overall, 499 participants received these pharmacotherapies while 444 participants received a placebo preparation or a non-absorbable disaccharide. We classified eight of the 11 trials as at 'high risk of bias' and downgraded the certainty of the evidence to very low for all outcomes.

Eleven trials, involving 943 participants, reported mortality data, although there were no events in five trials. Our analyses found no beneficial or harmful effects of sodium benzoate versus non-absorbable disaccharides (RR 1.26, 95% CI 0.49 to 3.28; 101 participants; 2 trials; I^2 = 0%), glycerol phenylbutyrate versus placebo (RR 0.65, 95% CI 0.11 to 3.81; 178 participants; 1 trial), ornithine phenylacetate versus placebo (RR 0.73, 95% CI 0.35 to 1.51; 269 participants; 2 trials; I^2 = 0%), AST-120 versus lactulose (RR 1.05, 95% CI 0.59 to 1.85; 41 participants; 1 trial), or polyethylene glycol versus lactulose (RR 0.50, 95% CI 0.09 to 2.64; 190 participants; 3 trials; I^2 = 0%).

Seven trials involving 521 participants reported data on hepatic encephalopathy. Our analyses showed a beneficial effect of glycerol phenylbutyrate versus placebo (RR 0.57, 95% CI 0.36 to 0.90; 178 participants; 1 trial; number needed to treat for an additional beneficial outcome (NNTB) 6), and of polyethylene glycol versus lactulose (RR 0.19, 95% CI 0.08 to 0.44; 190 participants; 3 trials; NNTB 4). We did not observe beneficial effects in the remaining three trials with extractable data: sodium benzoate versus non-absorbable disaccharides (RR 1.22, 95% CI 0.51 to 2.93; 74 participants; 1 trial); ornithine phenylacetate versus placebo (RR 2.71, 95% CI 0.12 to 62.70; 38 participants; 1 trial); or AST-120 versus lactulose (RR 1.05, 95% CI 0.59 to 1.85; 41 participants; 1 trial).

Ten trials, involving 790 participants, reported a total of 130 serious adverse events. Our analyses found no evidence of beneficial or harmful effects of sodium benzoate versus non-absorbable disaccharides (RR 1.08, 95% CI 0.44 to 2.68; 101 participants; 2 trials), glycerol phenylbutyrate versus placebo (RR 1.63, 95% CI 0.85 to 3.13; 178 participants; 1 trial), ornithine phenylacetate versus placebo (RR 0.92, 95% CI 0.62 to 1.36; 264 participants; 2 trials; I^2 = 0%), or polyethylene glycol versus lactulose (RR 0.57, 95% CI 0.18 to 1.82; 190 participants; 3 trials; I^2 = 0%). Likewise, eight trials, involving 782 participants, reported a total of 374 non-serious adverse events and again our analyses found no beneficial or harmful effects of the pharmacotherapies under review when compared to placebo or to lactulose/lactitol.

Nine trials, involving 733 participants, reported data on blood ammonia. We observed significant reductions in blood ammonia in placebo-controlled trials evaluating sodium benzoate (MD −32.00 µg/dL, 95% CI −46.85 to −17.15; 16 participants; 1 trial), glycerol phenylbutyrate (MD −12.00 µmol/L*week, 95% CI −23.37 to −0.63; 178 participants; 1 trial), ornithine phenylacetate (MD −27.10 µmol/L, 95% CI −48.55 to −5.65; 231 participants; 1 trial), and AST-120 (MD −22.00 µg/dL, 95% CI −26.75 to −17.25; 98 participants; 1 trial). However, there were no significant differences in blood ammonia concentrations in comparison with lactulose/lactitol with sodium benzoate (MD 9.00, 95% CI −1.10 to 19.11; 85 participants; 2 trials; I^2 = 0%), AST-120 (MD 5.20 units not specified, 95% CI −2.75 to 13.15; 35 participants; 1 trial), and polyethylene glycol (MD −29.28 µmol/L, 95% CI −95.96 to 37.39; 90 participants; 2 trials; I^2 = 88%).

Five trials received support from pharmaceutical companies while four did not; two did not provide this information.

Authors' conclusions

There is insufficient evidence to determine the effects of these pharmacotherapies on the prevention and treatment of hepatic encephalopathy in adults with cirrhosis. They have the potential to reduce blood ammonia concentrations when compared to placebo, but their overall effects on clinical outcomes of interest and the potential harms associated with their use remain uncertain. Further evidence is needed to evaluate the potential beneficial and harmful effects of these pharmacotherapies in this clinical setting.

PLAIN LANGUAGE SUMMARY

Drug treatments that specifically target ammonia for adults with cirrhosis and hepatic encephalopathy

Background

Cirrhosis is a chronic disorder of the liver. People with cirrhosis may develop hepatic encephalopathy, a condition that results in poor brain functioning. Some people with hepatic encephalopathy show clear evidence of brain dysfunction and are said to have 'overt' hepatic encephalopathy. They may have a poor memory, difficulty concentrating, speech problems, a tremor, particularly of their hands,

or stiffness of their limbs. These changes may occur in bouts or may be persistent. Other people with cirrhosis may not show any obvious signs of brain dysfunction, but some aspects of their brain function, such as attention and the ability to perform complex tasks are found to be impaired when tested. They are said to have 'minimal' hepatic encephalopathy. The reason why people develop hepatic encephalopathy is complex, but the build up in the blood of toxins from the gut, particularly of a compound called ammonia, plays a key role. Certain drugs have been developed specifically to lower blood ammonia levels and may help prevent people from developing hepatic encephalopathy and have beneficial effects in those already suffering from this disorder. However, the evidence that they are beneficial is unclear. The five drugs (pharmacotherapies) considered in this review are sodium benzoate, glycerol phenylbutyrate, ornithine phenylacetate, AST-120 (spherical carbon adsorbent), and polyethylene glycol.

Review question

We investigated the use of five pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. We did this by reviewing clinical trials in which people with cirrhosis were randomly allocated to treatment with one of these drugs or to an inactive dummy (placebo), to no treatment or to other drugs that are also used to manage this condition, such as, lactulose and lactitol (these are non-absorbable disaccharides). We included people with cirrhosis who had minimal or overt hepatic encephalopathy and people who were at risk of developing this complication.

Search date

5 March 2019

Study funding sources

Five of the 11 randomised clinical trials we included in the review received support from pharmaceutical companies. Two trials did not provide information on potential financial support or links to pharmaceutical companies. Four trials did not receive funding or other support from this source.

Study characteristics

We identified 11 randomised clinical trials comparing drugs that specifically target ammonia with inactive placebo or a non-absorbable disaccharide; two trials evaluated prevention of hepatic encephalopathy while nine trials evaluated treatment of hepatic encephalopathy. The trials assessed sodium benzoate (three trials), glycerol phenylbutyrate (one trial), ornithine phenylacetate (two trials), AST-120 (two trials) and polyethylene glycol (three trials). Participants were treated for varying periods ranging from five days to 16 weeks.

Key results

Sodium benzoate, glycerol phenylbutyrate, ornithine phenylacetate, and AST-120 lowered blood ammonia levels when compared to placebo, but none of the drugs lowered the blood ammonia levels when compared to a non-absorbable disaccharide. Glycerol phenylbutyrate seemed to have a beneficial effect on hepatic encephalopathy when compared to placebo, as did polyethylene glycol when compared to lactulose. None of the drugs appeared to affect the risk of death and did not have any notable adverse effects.

Quality of the evidence

The evidence we found was very uncertain, and so we are not confident that these drugs are useful for preventing or treating hepatic encephalopathy in people with cirrhosis. There were very few trials available, and not all of them provided sufficient data for us to include in our analyses. In addition, many of the published trials received support from the pharmaceutical industry which introduces an element of bias. Thus, we need more information to obtain a better idea if these drugs are useful and safe for use in this context.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Phamacotherapies that specifically target ammonia versus placebo or non-absorbable disaccharides for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis

1. Sodium benzoate compared to placebo for the treatment of hepatic encephalopathy in adults with cirrhosis

Patient or population: adults with cirrhosis and hepatic encephalopathy
Setting: hospital
Intervention: sodium benzoate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)[a]	Comments
	Risk with placebo	**Risk with sodium benzoate**				
All-cause mortality	Study population		not estimable	16 (1 RCT)	⊕◯◯◯ Very low	
	0 per 1000	0 per 1000 (0 to 0)				
Hepatic encephalopathy	No data reported					
Serious adverse events	Study population		not estimable	16 (1 RCT)	⊕◯◯◯ Very low	
	0 per 1000	0 per 1000 (0 to 0)				
Non-serious adverse events	Study population		not estimable	16 (1 RCT)	⊕◯◯◯ Very low	
	0 per 1000	0 per 1000 (0 to 0)				
Health-related quality of life	No data reported					

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Blood ammonia concentrations (µg/dL)	-	MD 32 lower (46.85 lower to 17.15 lower)	-	16 (1 RCT)	⊕○○○ Very low	

2. Sodium benzoate compared to non-absorbable disaccharides for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis

Participants: people with cirrhosis and hepatic encephalopathy
Setting: hospital
Intervention: sodium benzoate
Comparison: non-absorbable disaccharides (lactulose or lactitol)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)[b]	Comments
	Risk with lactulose/ lactitol	Risk with sodium benzoate				
All-cause mortality	Study population		RR 1.26 (0.49 to 3.28)	101 (2 RCTs)	⊕○○○ Very low	
	118 per 1000	148 per 1000 (58 to 386)				
Hepatic encephalopathy	Study population		RR 1.22 (0.51 to 2.93)	74 (1 RCT)	⊕○○○ Very low	
	194 per 1000	237 per 1000 (99 to 570)				
Serious adverse events	Study population		RR 1.08 (0.44 to 2.68)	101 (2 RCTs)	⊕○○○ Very low	
	137 per 1000	148 per 1000 (60 to 368)				
Non-serious adverse events	Study population		RR 1.13 (0.96 to 1.32)	182 (2 RCTs)	⊕○○○ Very low	
	469 per 1000	530 per 1000 (450 to 619)				

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Health-related quality of life	No data reported				
Blood ammonia concentrations	-	MD 9 higher (1.10 lower to 19.11 higher)	-	85 (2 RCTs)	⊕◯◯◯ Very low

3. Glycerol phenylbutyrate compared to placebo for the prevention of hepatic encephalopathy in adults with cirrhosis

Participants: people with cirrhosis and at least two previous episodes of hepatic encephalopathy in the previous 6 months
Setting: outpatients
Intervention: glycerol phenylbutyrate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)[c] Comments
	Risk with placebo	Risk with glycerol phenylbutyrate			
All-cause mortality	Study population		RR 0.65 (0.11 to 3.81)	178 (1 RCT)	⊕◯◯◯ Very low
	34 per 1000	22 per 1000 (4 to 130)			
Hepatic encephalopathy	Study population		RR 0.57 (0.36 to 0.90)	178 (1 RCT)	⊕◯◯◯ Very low
	409 per 1000	233 per 1000 (147 to 368)			
Serious adverse events	Study population		RR 1.63 (0.85 to 3.13)	178 (1 RCT)	⊕◯◯◯ Very low
	136 per 1000	222 per 1000 (116 to 427)			
Non-serious adverse events	Study population		RR 1.04 (0.88 to 1.21)	178 (1 RCT)	⊕◯◯◯ Very low

	761 per 1000	792 per 1000 (670 to 921)			
Health-related quality of life	No data reported				
Blood ammonia concentrations (µmol/L*week)	-	MD 12 lower (23.37 lower to 0.63 lower)	-	178 (1 RCT)	⊕◯◯◯ Very low

4. Ornithine phenylacetate compared to placebo for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis and hepatic encephalopathy

Participants: adults with cirrhosis and an acute episode of hepatic encephalopathy or adults with cirrhosis presenting with an episode of acute upper gastrointestinal bleeding
Setting: hospital
Intervention: ornithine phenylacetate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)[d] Comments
	Risk with placebo	Risk with ornithine phenylacetate			
All-cause mortality	Study population		RR 0.73 (0.35 to 1.51)	269 (2 RCTs)	⊕◯◯◯ Very low
	113 per 1000	82 per 1000 (39 to 170)			
Hepatic encephalopathy	Study population		RR 2.71 (0.12 to 62.70)	38 (1 RCT)	⊕◯◯◯ Very low
	0 per 1000	0 per 1000 (0 to 0)			
Serious adverse events	Study population		RR 0.92 (0.62 to 1.36)	264 (2 RCTs)	⊕◯◯◯ Very low

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	285 per 1000	262 per 1000 (176 to 387)				
Non-serious adverse events	Study population		RR 1.08 (0.78 to 1.51)	269 (2 RCTs)	⊕◯◯◯ Very low	
	368 per 1000	398 per 1000 (287 to 556)				
Health-related quality of life	No data reported					
Blood ammonia concentrations (µmol/L)	-	MD 27.1 lower (48.55 lower to 5.65 lower)	-	231 (1 RCT)	⊕◯◯◯ Very low	

5. AST-120 compared to placebo for the treatment of hepatic encephalopathy in adults with cirrhosis

Participants: adults with cirrhosis and hepatic encephalopathy
Setting: hospital
Intervention: AST-120
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)[e]	Comments
	Risk with placebo	Risk with AST-120				
All-cause mortality	Study population		not estimable	148 (1 RCT)	⊕◯◯◯ Very low	
	0 per 1000	0 per 1000 (0 to 0)				
Hepatic encephalopathy	No data reported					
Serious adverse events	No data reported					

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Non-serious adverse events	No data reported				
Health-related quality of life	No data reported				
Blood ammonia concentrations (µg/dL)	-	MD 22 lower (26.75 lower to 17.25 lower)	-	98 (1 RCT)	⊕◯◯◯ Very low	We were not able to gather data on blood ammonia concentration separately for the two treatment groups

6. AST-120 compared to non-absorbable disaccharide (lactulose) for the treatment of hepatic encephalopathy in adults with cirrhosis

Patient or population: adults with cirrhosis and hepatic encephalopathy
Setting: hospital
Intervention: AST-120
Comparison: lactulose

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)^f	Comments
	Risk with lactulose	Risk with AST-120				
All-cause mortality	Study population		RR 1.05 (0.59 to 1.85)	41 (1 RCT)	⊕◯◯◯ Very low	
	524 per 1000	550 per 1000 (0 to 0)				
Hepatic encephalopathy	Study population		RR 1.05 (0.59 to 1.85)	41 (1 RCT)	⊕◯◯◯ Very low	
	524 per 1000	550 per 1000 (309 to 969)				
Serious adverse events	Study population		not estimable	41 (1 RCT)	⊕◯◯◯ Very low	

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	0 per 1000	0 per 1000 (0 to 0)				
Non-serious adverse events	No data reported					
Health-related quality of life	No data reported					
Blood ammonia concentrations (units unspecified)	-	MD 5.2 higher (2.75 lower to 13.15 higher)	-	35 (1 RCT)	⊕○○○ Very low	We were only able to gather data on blood ammonia concentrations on a subgroup of participants

7. Polyethylene glycol compared non-absorbable disaccharide (lactulose) for the treatment of hepatic encephalopathy in adults with cirrhosis

Participants: adults with cirrhosis and hepatic encephalopathy
Setting: hospital
Intervention: polyethylene glycol
Comparison: lactulose

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)*g*	Comments
	Risk with lactulose	Risk with polyethylene glycol				
All-cause mortality	Study population		RR 0.50 (0.09 to 2.64)	190 (3 RCTs)	⊕○○○ Very low	
	43 per 1000	21 per 1000 (4 to 112)				
Hepatic encephalopathy	Study population		RR 0.19 (0.08 to 0.44)	190 (3 RCTs)	⊕○○○ Very low	

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	330 per 1000	63 per 1000 (26 to 145)			
Serious adverse events	Study population		RR 0.57 (0.18 to 1.82)	190 (3 RCTs)	⊕◯◯◯ Very low
	74 per 1000	42 per 1000 (13 to 136)			
Non-serious adverse events	Study population		RR 0.71 (0.40 to 1.27)	117 (2 RCTs)	⊕◯◯◯ Very low
	191 per 1000	136 per 1000 (77 to 243)			
Health-related quality of life	No data reported				
Blood ammonia levels (µmol/L)	-	MD 29.28 lower (95.96 lower to 37.39 higher)	-	90 (2 RCTs)	⊕◯◯◯ Very low

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **RCT:** randomised clinical trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]We downgraded the evidence by three levels because of the serious risk of bias (two levels) and uncertainty; only one small trial is included in the analysis and there were no reported events (one level).
[b]We downgraded the evidence by three levels because of the serious risk of bias; only one of the two trials had a low risk of bias (two levels) and uncertainty; only two small trials are included in the analysis (one level).
[c]We downgraded the evidence by three levels because of the serious risk of bias (two levels) and uncertainty; only one small trial is included in the analysis (one level).

^{d}We downgraded the evidence by three levels because of the serious risk of bias (two levels) and uncertainty; only two small trials are included in the analysis (one level).

^{e}We downgraded the evidence by three levels because of the serious risk of bias (two levels) and uncertainty; only one small trial is included in the analyses, there were no reported deaths and the blood ammonia data were incomplete (one level).

^{f}We downgraded the evidence by three levels because of the serious risk of bias (two levels) and uncertainty (only one small trial is included in the analyses; there were no reported deaths and the blood ammonia data were incomplete) (one level).

^{g}We downgraded the evidence by three levels because of the serious risk of bias (two levels) and uncertainty; only two small trials are included in the analyses (one level).

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BACKGROUND

Description of the condition

The term 'hepatic encephalopathy' is used to describe the spectrum of neuropsychiatric change that can arise in people with cirrhosis. The joint guideline from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) defines hepatic encephalopathy as, "brain dysfunction associated with liver insufficiency or portal-systemic shunting" (AASLD/EASL 2014; Vilstrup 2014).

Clinically apparent or 'overt' hepatic encephalopathy manifests as a neuropsychiatric syndrome encompassing a wide spectrum of mental and motor disorders (Ferenci 2002; Weissenborn 1998). It may develop over a period of hours or days, apparently spontaneously, or else, in 50% to 70% of instances, follow an identifiable precipitating event such as gastrointestinal bleeding, infection, dehydration, or constipation (Pantham 2017). Episodes may recur. Between episodes, people may return to their baseline neuropsychiatric status or retain a degree of impairment (Bajaj 2010). Less frequently, people present with persistent neuropsychiatric abnormalities, which are always present to some degree, but which may fluctuate in severity (Ferenci 2002). The changes in mental state in people with overt hepatic encephalopathy range from subtle alterations in personality, intellectual capacity and cognitive function to deep coma. The changes in motor function may include asterixis (flapping tremor), rigidity, speech disorders, tremor, and delayed diadochocinetic movements (Cadranel 2001; Victor 1965; Weissenborn 1998). People with overt hepatic encephalopathy may show other associated abnormalities, including: impaired psychomotor performance (Schomerus 1998); disturbed neurophysiological function (Chu 1997; Parsons-Smith 1957); altered cerebral neurochemical/neurotransmitter homeostasis (Taylor-Robinson 1994); reductions in global and regional cerebral blood flow and metabolism (O'Carroll 1991); and changes in cerebral fluid homeostasis (Haussinger 2000). In general, the degree of impairment in these variables increases with the severity of the underlying liver disease (Bajaj 2009). 'Minimal' hepatic encephalopathy, in the older literature referred to as 'subclinical' or 'latent' hepatic encephalopathy, is the term applied to people with cirrhosis with no clinical neuropsychiatric abnormalities who, nevertheless, show abnormalities in neuropsychometric or neurophysiological performance, when tested (Ferenci 2002; Guérit 2009). Recently, the term *covert* hepatic encephalopathy has been introduced to encompass patients with minimal hepatic encephalopathy and those with low-grade overt hepatic encephalopathy. While this approach may be pragmatic, it is not clear how informative or valuable it is in clinical and particularly research settings. Indeed, it has already been shown that patients classified as having covert hepatic encephalopathy behave, when tested, as two relatively independent groups (Montagnese 2014; Zacharias 2017).

There is no gold standard test for the diagnosis of hepatic encephalopathy (AASLD/EASL 2014; Montagnese 2004; Vilstrup 2014), but rather a range of diagnostic tests that can be used singly or in combination. A detailed neuropsychiatric history and examination (Montagnese 2004), should be undertaken with particular attention paid to changes in memory, concentration, cognition, and consciousness. Clinicians and researchers often use the West Haven Criteria to grade mental status (Conn 1977), and the Glasgow Coma Score to grade the level of consciousness (Teasdale 1974). The history and examination will identify the clinical features suggestive of hepatic encephalopathy, which are often subtle, or confirm their absence. Further, they will allow exclusion of other causes of neuropsychiatric abnormalities, such as certain neurological disorders and other metabolic encephalopathies, including those associated with diabetes, renal failure, and chronic pulmonary insufficiency. People with hepatic encephalopathy also show impaired performance on a range of psychometric tests (Montagnese 2004; Randolph 2009). Those with minimal hepatic encephalopathy show deficits in attention, visuospatial abilities, fine motor skills, and memory, while other cognitive functions are relatively well preserved. People with overt hepatic encephalopathy show additional disturbances in psychomotor speed, executive function, and concentration. Several paper and pencil psychometric tests are used in the evaluation of cognitive performance in people suspected of having hepatic encephalopathy. These tests are either used individually or are grouped together into test batteries or systems. Of the tests used singly, Number Connection Tests A and B are the best known (Ferenci 2002). The Psychometric Hepatic Encephalopathy Score (PHES), which comprises five paper and pencil tests covering the domains of attention, visual perception, and visuo-constructive abilities, is the most widely used psychometric test battery and has high diagnostic specificity (Schomerus 1998; Weissenborn 2001). PHES test scores have to be normalised to take account of factors such as age, sex, and educational level. At present, normative databases are available in several countries, including Germany, Italy, Spain, Mexico, Korea, Romania, India, and the UK. In countries where levels of illiteracy are high, Figure Connection Tests A and B are often used either alone or as part of the PHES battery (Dhiman 1995). People with hepatic encephalopathy may also show several neurophysiological abnormalities (Guérit 2009). The electroencephalogram (EEG), which primarily reflects cortical neuronal activity, may show progressive slowing of the background activity and abnormal wave morphology (Parsons-Smith 1957). Recent advances in electroencephalogram analysis provide better quantifiable and more informative data (Jackson 2016; Olesen 2016). The brain responses, or evoked potentials, to stimuli such as light and sound may show abnormal slowing or wave forms, or both (Chu 1997; Guérit 2009). Other potential diagnostic techniques, such as the Critical Flicker Fusion Frequency (Kircheis 2002), the Inhibitory Control Test (Bajaj 2008), and the Stroop test (Allampati 2016), need further validation. Blood ammonia concentrations

are not routinely measured to diagnose hepatic encephalopathy (Blanco Vela 2011; Lockwood 2004), but are often monitored in clinical trials.

Description of the intervention

We assessed five separate pharmacotherapies that specifically target ammonia. These differed in their formulation, routes of administration, and modes of action (Table 1).

How the intervention might work

The exact pathogenesis of hepatic encephalopathy is unknown but ammonia is known to play a key role (Butterworth 2013; Morgan 2018). Ammonia is produced in the intestine from dietary protein, deamination of glutamine via glutaminase and bacterial action in the colon. It is absorbed by non-ionic diffusion but specific ammonia transporters may also be involved; ammonia concentrations in the portal vein are ten-fold higher than in arterial blood. The hepatic extraction rate is high. The ammonia in portal blood, together with the ammonia derived from hepatic amino acid metabolism, is taken up primarily by periportal hepatocytes and metabolised to urea via the urea cycle. The kidneys and muscles also play a role in ammonia homeostasis (Wright 2011). In skeletal muscle, ammonia is transformed into glutamine through the action of glutamine synthetase. In the kidneys, ammonia is generated from the deamination of glutamine. In people with cirrhosis, blood ammonia levels increase primarily because of a reduction in first-pass metabolism of ammonia as a result of portal systemic shunting and a loss of hepatic metabolic capacity. As a result, gut-derived ammonia is not effectively cleared from the blood by the liver; it consequently enters the systemic circulation and impinges on the brain where it has both direct and indirect effects on cerebral function. Treatment is aimed, primarily, at reducing the production and absorption of ammonia from the gastrointestinal tract and this is usually affected by use of non-absorbable disaccharides and non-absorbable antibiotics.

Hyperammonaemia is also a major consequence of genetic disorders of the urea cycle enzymes. In these conditions the increase in blood ammonia concentrations results directly from failure of hepatic ammonia metabolism. Treatment is based on providing alternative pathways for the removal of nitrogen waste (Berry 2014). A small number of drugs, so-called 'ammonia scavengers', have been developed for use in urea cycle disorders. The best known of these agents are sodium benzoate, and sodium/glycerol phenylbutyrate. Both decrease ammonia concentrations by serving as alternatives to urea for the excretion of waste nitrogen. Benzoate conjugates with glycine to form hippuric acid while phenylacetate conjugates with glutamine in the liver and kidneys to form phenylacetylglutamine. Hippuric acid and phenylacetylglutamine are subsequently excreted in the urine (Table 1). These 'ammonia scaveng-

ing agents' have also been used to treat hepatic encephalopathy in people with cirrhosis (Campollo 1992; Efrati 2000; Gonzalez 1994; Mendenhall 1986; Misel 2013; Rockey 2014; Sushma 1992; Uribe 1990; Weiss 2018). Ornithine phenylacetate was specifically developed for the treatment of hepatic encephalopathy in people with cirrhosis; the L-ornithine moiety acts as a substrate for the synthesis of glutamine from ammonia in skeletal muscle, while the phenylacetate moiety combines with glutamine to form phenylacetylglutamine, which is excreted in the urine (Jalan 2007; Rahimi 2016; Rose 2012; STOP-HE 2017; Ventura-Cots 2016). This agent is not intended for use in the treatment of urea cycle enzyme disorders (Rahimi 2016). AST-120 is a carbon microsphere adsorbent that differs structurally from activated charcoal in that it has a selective binding surface. It exhibits superior adsorption of low molecular weight organic compounds such as ammonia from the lumen of the lower gastrointestinal tract, which are then excreted in the faeces (Bajaj 2013; Bosoi 2011; Pockros 2009). Polyethylene glycol (PEG) is a cathartic; it causes rapid clearance of the gut bacteria that synthesize ammonia, thereby reducing its production (Naderian 2017; Rahimi 2014; Rahimi 2016). The adverse events associated with the use of these drugs are mainly gastrointestinal and include diarrhoea, constipation, dry mouth, and changes in appetite (Lee 2010; Rahimi 2016).

Why it is important to do this review

Hepatic encephalopathy is a common and debilitating complication of cirrhosis. Approximately 10% to 14% of people with cirrhosis have overt hepatic encephalopathy when they are first diagnosed with liver disease (Saunders 1981). In people with decompensated cirrhosis, the prevalence of overt hepatic encephalopathy at presentation is about 20% (D'Amico 1986; De Jongh 1992; Zipprich 2012). In people with cirrhosis who have no evidence of neuropsychiatric impairment, the risk of developing an episode of overt hepatic encephalopathy within five years of presentation varies from 5% to 25%, depending on the presence or absence of other risk factors; the cumulative incidence of overt hepatic encephalopathy is as high as 40% (Bajaj 2011a; Randolph 2009). The prevalence of minimal hepatic encephalopathy may be more than 50% in people with previous overt hepatic encephalopathy (Lauridsen 2011; Sharma 2010).

The presence of hepatic encephalopathy, whether minimal or overt, is associated with significant impairment in the performance of complex tasks, such as driving (Kircheis 2009; Schomerus 1981), and a detrimental effect on quality of life (Groeneweg 1998), and safety (Roman 2011). In addition, the presence of overt hepatic encephalopathy pre-transplantation has a detrimental effect on neurocognitive function post-transplantation (Sotil 2009), and on survival (Bustamante 1999; D'Amico 2006; Jepsen 2010; Stewart 2007). The one-year survival rate in people who have hepatic encephalopathy at presentation is 36%, with a five-year survival rate of 15% (Jepsen 2010), while the survival prob-

ability after a first episode of hepatic encephalopathy is 42% at one year but only 23% at three years (Bustamante 1999). Overt hepatic encephalopathy also poses a substantial burden for the affected families (Bajaj 2011b), and a significant financial burden on healthcare systems (Poodad 2007; Stepanova 2012).

Strategies to prevent and treat hepatic encephalopathy in people with cirrhosis are clearly needed (Morgan 2018). At present, treatment is directed primarily at reducing the production and absorption of gut-derived neurotoxins, particularly ammonia, mainly through dietary manipulation, bowel cleansing, non-absorbable disaccharides and non-absorbable antibiotics (AASLD/ EASL 2014; Vilstrup 2014). Interventions that specifically target the metabolism and elimination of ammonia may provide new treatment options (Jover-Cobos 2013; McGuire 2010; Rahimi 2016; Rose 2012). There are several potential candidates (Table 1). Some, for example, sodium benzoate and glycerol phenylbutyrate, are used to treat the hyperammonaemia associated with urea cycle enzyme deficiencies; they serve as 'ammonia scavengers', providing alternative, non-urea cycle pathways for removal of ammonia. Ornithine phenylacetate is also an ammonia scavenger; it was developed specifically for the treatment of hepatic encephalopathy in people with cirrhosis. AST-120 and polyethylene glycol speed elimination of ammonia or ammonia-generating bacteria via the large intestine (Table 1). None of these pharmacotherapies are currently licensed for the indication of hepatic encephalopathy, although several are undergoing phase IIB and III clinical trials. Thus, presently these agents do not have a place in routine clinical practice.

Very little is known about the potential beneficial and harmful effects of these pharmacotherapies. We have, therefore, conducted a systematic review with meta-analyses of the available randomised clinical trials of five pharmacotherapeutic agents that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in people with cirrhosis, following recommendations for best practice.

O B J E C T I V E S

To evaluate the beneficial and harmful effects of pharmacotherapies that specifically target ammonia versus placebo, no intervention, or other active interventions, for the prevention and treatment of hepatic encephalopathy in people with cirrhosis.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials, irrespective of blinding, language, or publication status in our primary analyses. If, during the selection of trials, we identified observational studies, for example, quasi-randomised studies, cohort studies or patient reports that described adverse events caused by or associated with use of the interventions under review, then we included these data in our qualitative analyses. We did not specifically search for observational studies for inclusion in this review, which is a known limitation.

Types of participants

We included adults with cirrhosis and minimal or overt hepatic encephalopathy, or adults who were at risk of developing overt hepatic encephalopathy. We included participants in our primary analyses irrespective of age, sex, the aetiology and severity of the underlying liver disease, or the presence or absence of precipitating factors. We excluded trials involving people with hepatic encephalopathy associated with acute liver failure. We included trials involving people with hepatic encephalopathy associated with either cirrhosis or non-cirrhotic portal hypertension provided that subgroup analyses were available or else the proportion of participants with non-cirrhotic portal hypertension was very small.

Types of interventions

We evaluated drugs that specifically target ammonia, including sodium benzoate, glycerol phenylbutyrate, ornithine phenylacetate, spherical carbon adsorbents (AST-120), and polyethylene glycol versus placebo, no treatment or interventions that have a potentially beneficial effect on hepatic encephalopathy, such as the non-absorbable disaccharides (Gluud 2016). We included trials irrespective of the dose, treatment duration, or mode of administration of the drugs under review. We allowed co-interventions if they were administered equally to all comparison groups.

We did not include trials involving use of L-ornithine L-aspartate as these are the subject of a separate Cochrane Review (Goh 2018).

Types of outcome measures

We assessed all outcomes at the maximum duration of follow-up.

Primary outcomes

1. All-cause mortality.
2. Hepatic encephalopathy. We assessed this outcome using the primary investigators' overall assessment of: i) the number of participants who developed hepatic encephalopathy, and ii) the number of participants without a clinically-relevant improvement in hepatic encephalopathy.
3. Serious adverse events. We defined adverse events as any untoward medical occurrence (ICH-GCP 1997) and considered adverse events as serious if they resulted in death; were life-threatening; required inpatient hospitalisation or prolongation of

existing hospitalisation; or resulted in persistent or significant disability or incapacity. In this review, serious adverse events included mortality and hepatic encephalopathy, and they were analysed as a composite outcome.

Secondary outcomes

1. Non-serious adverse events. We considered as non-serious all adverse events that did not fulfil the criteria for serious adverse events, as described above (ICH-GCP 1997).
2. Health-related quality of life.
3. Blood ammonia.

Search methods for identification of studies

We combined the electronic and manual searches.

Electronic searches

We searched the Cochrane Hepato-Biliary Specialised Register (March 2019: hbg.cochrane.org/specialised-register), the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 3) in the Cochrane Library; MEDLINE Ovid (1946 to March 2019); Embase Ovid (1974 to March 2019); LILACs (Bireme; 1982 to March 2019); Science Citation Index Expanded (Web of Science; 1900 to March 2019); and Conference Prodeedings Citation Index - Science (Web of Science; 1990 to March 2019; Royle 2003) using the strategies outlined in Appendix 1. We did not have access to Chinese, Russian, or Japanese databases, but we plan to search these in future updates should they become available to us via the Cochrane Hepato-Biliary Group.

Searching other resources

We searched the reference lists of papers identified in the electronic searches and wrote to authors of the identified clinical trials and relevant pharmaceutical companies for additional data, if required. We searched the conference proceedings of the annual meetings of the British Society of Gastroenterology (BSG), the European Association for the Study of the Liver (EASL), the United European Gastroenterology Week (UEGW), the American Gastroenterological Association (AGA), and the American Association for the Study of Liver Diseases (AASLD) from 2000 to 2018/9. We searched online trials registries such as ClinicalTrials.gov (clinicaltrials.gov/); European Medicines Agency (EMA; www.ema.europa.eu/ema/); the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp), and the Food and Drug Administration (FDA; www.fda.gov) in March 2019. We also searched Google Scholar using the search terms cirrhosis AND ammonia scavenging agents; and pharmaceutical company sources for ongoing or unpublished trials with no date restriction.

Data collection and analysis

We performed the review following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), Cochrane Hepato-Biliary information for authors (hbg.cochrane.org/), and the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidelines (MECIR 2018).

Selection of studies

Three review authors (HDZ, APZ, and MYM), working independently, read the electronic search output, performed additional manual searches, and listed potentially eligible trials. All review authors read the potentially eligible trials and participated in the final selection of trials for inclusion. If trial data were reported in more than one publication, we selected the report with the largest number of participants and the longest duration of follow-up as our primary reference. We listed details of all the included trials in the Characteristics of included studies table, and listed all the excluded trials with the reasons for their exclusion in the Characteristics of excluded studies table. A fourth review author (LLG) acted as ombudsman in case of disagreements on trial suitability for inclusion or exclusion. We resolved contrary opinions through discussion.

Data extraction and management

All review authors independently extracted data and evaluated bias. We requested missing data and other information from the published trial reports from the corresponding authors of the included trials. We sought information and data from identified but unpublished trials or ongoing trials from the principal investigators and sponsors. We gathered the following data from the included trials.

- **Trials:** design (cross-over or parallel); settings (number of clinical sites; outpatient or inpatient; inclusion period); country of origin; publication status; funding sources;
- **Participants:** mean age; proportion of men; aetiology and severity of the liver disease; type of hepatic encephalopathy (diagnostic criteria and definitions/terminology); previous history of hepatic encephalopathy;
- **Interventions:** type, dose, duration of therapy, mode of administration; co-interventions;
- **Outcomes:** including definitions used in the assessment and duration of follow-up; number of participants included in the assessment of outcomes (number of losses to follow-up/ withdrawals); outcomes included in the meta-analyses.

Assessment of risk of bias in included studies

We followed Cochrane Hepato-Biliary recommendations for assessing the risk of bias in the included trials, based on the definitions described below (hbg.cochrane.org/information-authors).

We assessed each domain separately as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017) and combined the domains to provide an overall assessment of bias control for both mortality and non-mortality outcomes. We classified trials as low risk of bias only if none of the domains was designated as being at unclear or high risk of bias.

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 were adequate if performed by an independent person not otherwise involved in the trial.

• Unclear risk of bias: the method of sequence generation was not specified.

• High risk of bias: sequence generation method was not random.

Allocation concealment

• Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment; allocation was controlled by a central and independent randomisation unit or similar adequate method (e.g. serially numbered opaque sealed envelopes) to ensure that the allocation sequence was unknown to the investigators (Savović 2012a; Savović 2012b).

• Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.

• High risk of bias: 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 performed adequately using a placebo. We defined lack of blinding as not likely to affect the evaluation of mortality (Savović 2012a; Savović 2012b).

• Unclear risk of bias: insufficient information to assess blinding.

• High risk of bias: no blinding or incomplete blinding.

Blinding of outcome assessors

• Low risk of bias: blinding of outcome assessors performed adequately using a placebo. We defined lack of blinding as not likely to affect the evaluation of mortality (Savović 2012a; Savović 2012b).

• Unclear risk of bias: there was insufficient information to blinding.

• High risk of bias: no blinding or incomplete blinding.

Incomplete outcome data

• Low risk of bias: missing data were 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: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.

• 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 (all-cause mortality, hepatic encephalopathy, and serious adverse events). If we had access to the original trial protocol, the outcomes selected should be those called for in the 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: predefined relevant outcomes were not reported fully or the reporting was unclear.

• High risk of bias: one or more predefined outcomes were not reported.

Other bias

• Low risk of bias: the trial appeared free of other biases including: medicinal dosing, medicinal problems, or follow-up (as defined below).

• Unclear risk of bias: the trial may or may not have been free of other domains 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 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 above.

• High risk of bias: one or more of the bias domains was of unclear or high risk of bias.

Measures of treatment effect

We analysed dichotomous outcomes using risk ratios (RR) and continuous outcomes using mean differences (MD), both with

95% confidence intervals (CI). For primary outcomes, we calculated the number needed to treat for an additional beneficial outcome (NNTB) as 1 / risk difference (RD) based on the highest-quality evidence (randomised clinical trials with a low risk of bias where available).

Unit of analysis issues

We included randomised clinical trials using a parallel-group design. We did not identify any multi-armed trials, however, if we identify any such trials in future updates, then we will undertake separate pair-wise comparisons of the treatments of interest. We did not identify any cross-over trials, however, if we identify any such trials in future updates, we will only use data from the first treatment period (Deeks 2017).

Dealing with missing data

We collected data on all participants randomised and included all participants irrespective of compliance or follow-up. We planned to evaluate the influence of missing data (Higgins 2008), by undertaking best-case scenario, worst-case scenario, and extreme worst-case scenario analyses (hbg.cochrane.org/information-authors). However, we did not identify any randomised clinical trials with missing outcome data.

Assessment of heterogeneity

We expressed heterogeneity as I^2 statistic values using the following thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and more than 80% (considerable). We used this information when describing and interpreting our analyses and included the information in the 'Summary of findings' table.

Assessment of reporting biases

We evaluated reporting bias based on the definition and reporting of key outcomes (the most clinically relevant) and by comparing protocols, online trial registrations, and trial publications if available. We planned to use visual inspection of funnel plots and regression analyses to evaluate reporting biases if our analysis included at least 10 trials with reported events for an individual pharmacotherapy (Egger 1997; Harbord 2006), however, our review did not reach this number threshold.

Data synthesis

We performed the analysis in Review Manager 5 (Review Manager 2014) and STATA version 14 (Stata 2015).

Meta-analyses

We analysed trials for each of the drugs that specifically target ammonia separately, using fixed-effect and random-effects meta-analyses (Deeks 2017). The individual meta-analyses included a small number of trials, and we did not identify differences between the two models. We chose to report random-effects meta-analyses based on an expected clinical difference between trials.

In the case that estimates of the random-effects and fixed-effect meta-analyses are similar in future updates, then we will assume that any small-study effect had 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 trials. If the larger trials 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 trials. Based on the expected clinical heterogeneity, we anticipated that a number of analyses would display statistical between-trial heterogeneity ($I^2 > 0\%$).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses to determine the influence of:
- risk of bias;
- type of encephalopathy;
- aetiology of the liver disease (alcohol or hepatitis).

We were not able to undertake subgroup analyses because the number of trials was too small.

Sensitivity analysis

We planned to undertake worst-case scenario analyses, as described in Dealing with missing data. However, outcome data sets were complete in the intervention and control groups in all of the included trials.

Trial Sequential Analysis

We planned to perform Trial Sequential Analyses of our primary outcomes to evaluate the risk of random error associated with sparse data and cumulative testing, and to evaluate futility (Higgins 2008; Wetterslev 2008). However, the number of events, participants, and trials were clearly insufficient, so we did not undertake these analyses.

In future updates of our review, if the data allow, we plan to undertake Trial Sequential Analyses with alpha 3%, power 90%, and the results of the random-effects meta-analyses (upper 95% CI) in order to determine the relative risk reduction and the control group event.

Certainty of evidence, GRADE

We used the GRADE system to evaluate the certainty of the evidence for all outcomes reported in the review, considering the within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimate, and risk of publication bias (Schünemann 2013).

'Summary of findings' tables

We used GradePro 2015 to generate a 'Summary of findings' table with information about outcomes, risk of bias, and the results of the meta-analyses (Summary of findings for the main comparison).

R E S U L T S

Description of studies

We included 11 randomised clinical trials (Characteristics of included studies), and excluded three observational trials, one randomised clinical trial comparing two agents that specifically target ammonia, and one randomised clinical trial in which the drug of interest was used as adjuvant therapy to another active agent (Characteristics of excluded studies). In addition, we identified two ongoing trials that may be eligible for inclusion in future updates (NCT00558038; NCT03448770). We did not have access to data from these ongoing trials. Four of the 11 trials were published in abstract form only (Bajaj 2013; Gonzalez 1994; Pockros 2009; STOP-HE 2017), while the remaining seven trials were published as full papers (Naderian 2017; Rahimi 2014; Rockey 2014; Shehata 2018; Sushma 1992; Uribe 1990; Ventura-Cots 2016).

We included 11 trials in our quantitative and qualitative analyses (Bajaj 2013; Gonzalez 1994; Naderian 2017; Pockros 2009; Rahimi 2014; Rockey 2014; Shehata 2018; STOP-HE 2017; Sushma 1992; Uribe 1990; Ventura-Cots 2016).

Results of the search

We identified 513 potentially relevant records from electronic databases, and 10 additional records through manual searches and enquires (Figure 1). After removing duplicate references and references that were irrelevant to this review, we identified 17 records reporting 11 randomised clinical trials that fulfilled our inclusion criteria (Bajaj 2013; Gonzalez 1994; Naderian 2017; Pockros 2009; Rahimi 2014; Rockey 2014; Shehata 2018; STOP-HE 2017; Sushma 1992; Uribe 1990; Ventura-Cots 2016). In five of the 11 trials the control group received a placebo preparation (Bajaj 2013; Gonzalez 1994; Rockey 2014; STOP-HE 2017; Ventura-Cots 2016); in the remaining six trials they received a non-absorbable disaccharide (Naderian 2017; Pockros 2009; Rahimi 2014; Shehata 2018; Sushma 1992; Uribe 1990). We did not identify any trials that compared these drugs with no treatment or with interventions that might potentially benefit hepatic encephalopathy, other than the non-absorbable disaccharides.

Figure 1. Study flow diagram

513 records identified through database searching

10 additional records identified through other sources (all 10 through manual searches of the literature)

377 records after duplicates removed

377 records screened

353 records excluded; reports of 2 additional trials excluded as ongoing

22 records assessed for eligibility

1 double-blind cross-over trial comparing two different ammonia scavengers; 3 observational studies; and 1 randomised cross-over trial excluded

17 records (11 trials) included in qualitative and quantitative analyses

The countries of origin were Egypt (Shehata 2018), India (Sushma 1992), Iran (Naderian 2017), Mexico (Gonzalez 1994; Uribe 1990), Spain (Ventura-Cots 2016), and the USA (Bajaj 2013; Pockros 2009; Rahimi 2014). One study was undertaken in centres in the USA, Ukraine, and Russia (Rockey 2014); one study was undertaken in centres in Australia, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Israel, Italy, Netherlands, New Zealand, Russia, Spain, and the USA (STOP-HE 2017).

Included studies

Participants

In total, 499 participants received pharmacotherapies that specifically target ammonia and 444 participants received placebo or a non-absorbable disaccharide. The mean age of participants in the included trials ranged from 35.6 to 59.6 years and the proportion of men from 41.7% to 79.0%. The proportion of participants with cirrhosis secondary to hepatitis B or C infection ranged from 4% to 100%; the proportion with alcohol-related cirrhosis ranged from 4.8% to 70%.

One trial, involving 38 participants with cirrhosis, evaluated prevention of hepatic encephalopathy following an upper gastrointestinal bleed (Ventura-Cots 2016); six participants had overt hepatic encephalopathy at the time of inclusion while the remaining 32 participants did not. One trial evaluated the secondary prevention of hepatic encephalopathy in participants who had had at least two previous episodes of hepatic encephalopathy Grade 2 or greater in the previous six months (Rockey 2014).

The remaining nine trials included participants with current hepatic encephalopathy which was classified as covert (minimal and Grade 1) in one trial (Bajaj 2013), and as overt (Grades 1 to 4) in eight (Gonzalez 1994; Naderian 2017; Pockros 2009; Rahimi 2014; Shehata 2018; STOP-HE 2017; Sushma 1992; Uribe 1990).

Interventions

Three trials evaluated sodium benzoate in doses of 5.6 to 10 g a day given orally or via a nasogastric tube (Gonzalez 1994; Sushma 1992; Uribe 1990); one trial evaluated oral glycerol phenylbutyrate 12 mL a day (Rockey 2014); two trials evaluated intravenous ornithine phenylacetate in doses ranging from 5 g to 20 g a day (STOP-HE 2017; Ventura-Cots 2016); two trials evaluated oral AST-120 in doses ranging from 6 g to 12 g a day (Bajaj 2013; Pockros 2009); and three trials evaluated polyethylene glycol given orally or via a nasogastric tube at a dose of 280 grams in 4 litres of water daily (Naderian 2017; Rahimi 2014), or three to four sachets at 64 grams per sachet dissolved in one litre of water, given

orally over three to four hours or via nasogastric tube at a rate of 20 to 30 millilitres per minute (Shehata 2018).

Comparisons

The control groups received either a placebo preparation (Bajaj 2013; Gonzalez 1994; Rockey 2014; STOP-HE 2017; Ventura-Cots 2016), or a non-absorbable disaccharide in a dose adjusted to produce two to three semi-soft stools per day (Naderian 2017; Pockros 2009; Rahimi 2014; Sushma 1992; Uribe 1990), or a fixed dose of 20-30 millilitres orally or via nasogastric tube, given as 3 doses over 24 hours with 200 millilitres as a retention enema every four hours (Shehata 2018).

Co-interventions

The majority of trials used co-interventions. It is unclear if one study used additional active agents, which included rifaximin, L-ornithine L-aspartate and lactulose, in similar proportions of participants in the treatment and placebo groups (STOP-HE 2017). Three trials did not report the use of co-interventions (Bajaj 2013; Naderian 2017; Shehata 2018). The remaining seven trials used co-interventions in similar proportions of participants in the treatment and control groups.

Outcomes

All 11 trials reported on mortality although there were no events in one trial (Gonzalez 1994). Ten trials reported the other primary outcomes (Bajaj 2013; Naderian 2017; Pockros 2009; Rahimi 2014; Rockey 2014; Shehata 2018; STOP-HE 2017; Sushma 1992; Uribe 1990; Ventura-Cots 2016). Investigators assessed hepatic encephalopathy using several different methods. Seven of 10 trials assessed mental status using West Haven Criteria (Bajaj 2013; Gonzalez 1994; Pockros 2009; Rockey 2014; Sushma 1992; Uribe 1990; Ventura-Cots 2016). They also used several composite assessment techniques (Table 2) including the Portal-Systemic Encephalopathy Sum and Index (Gonzalez 1994; Sushma 1992; Uribe 1990); the Hepatic Encephalopathy Scoring Algorithm (HESA) (Naderian 2017; Pockros 2009; Rahimi 2014; Shehata 2018; STOP-HE 2017); the Clinical Hepatic Encephalopathy Staging Scale (CHESS) (Ventura-Cots 2016); and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Bajaj 2013). One trial used visual, auditory, and somatosensory-evoked potentials as an additional test moiety (Sushma 1992), while the only trial that included participants with minimal hepatic encephalopathy used the Psychometric Hepatic Encephalopathy Score (PHES) test battery (Bajaj 2013).

Ten trials measured blood ammonia concentrations (Bajaj 2013; Gonzalez 1994; Naderian 2017; Pockros 2009; Rahimi 2014;

Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis (Review)

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Rockey 2014; STOP-HE 2017; Sushma 1992; Uribe 1990; Ventura-Cots 2016). However, we could not extract the data from one trial as they were displayed in graph form in the published paper and the corresponding data were not included separately in the text (Ventura-Cots 2016). Blood ammonia concentrations were measured variously in venous and arterial blood; the timing of the blood sampling varied between trials as did the laboratory measurement techniques and the expression of the results (Table 3)

Excluded studies

We excluded five trials (Campollo 1992; Ghabril 2013; Mendenhall 1986; Panella 1993; Weiss 2018). See Characteristics of excluded studies.

We excluded one trial because it did not meet our inclusion criteria in that it compared two oral interventions that specifically target ammonia: sodium benzoate or sodium phenylacetate (Mendenhall 1986); both agents were effective at improving or maintaining participants' mental status. We excluded one further trial because it did not meet our inclusion criteria in that it assessed sodium benzoate as an adjuvant to branched chain amino acids for the treatment of chronic stable hepatic encephalopathy versus placebo (Panella 1993); participants receiving adjuvant sodium benzoate showed a significantly greater reduction in blood ammonia concentrations compared to the group receiving placebo and a trend to a greater reduction in Number Connection Test times and the Portal-Systemic Encephalopathy Index.

We excluded three trials because they were observational. The first included 18 participants with cirrhosis and chronic persistent hepatic encephalopathy, given sodium benzoate in a mean dose of 6.4 grams daily for six months (Campollo 1992). Three participants were withdrawn within the first month of treatment with nausea and abdominal pain. The remaining 15 participants showed improvement in their Portal-Systemic Encephalopathy Sum and Index (Table 2). The second included 18 participants with overt hepatic encephalopathy and hyperammonaemia admitted to an intensive care unit, given sodium phenylbutyrate 200 mg/kg per day orally or via a nasogastric tube (Weiss 2018). They compared outcomes with those in an historical control group (matched for age, sex, MELD (Model for End-stage Liver Disease) score, and severity of hepatic encephalopathy using West Haven Criteria), managed in the same unit, using the same guidelines. Blood ammonia concentrations were lower at 12 and 48 hours in those receiving sodium phenylbutyrate, while survival on discharge from the intensive care unit was significantly higher. Several side effects were recorded in the participants who received sodium phenylbutyrate including ascites (two), leucopenia (one), pancreatitis (one), herpes simplex infection (one), and renal tubulopathy (one). In the control group, one participant developed ascites and one developed a maculopapular eruption. The third observational study included 15 participants with cirrhosis and a history of at least two previous episodes of overt hepatic encephalopathy within the previous six months, given 6mL of glycerol phenylbutyrate twice daily for one week followed by 9 mL twice daily for three weeks to assess tolerability and the effect on blood ammonia concentrations (Ghabril 2013). The lower of the two doses effectively reduced blood ammonia concentrations compared with baseline and was better tolerated.

Risk of bias in included studies

We based our 'Risk of bias' assessment on the published descriptions combined with additional information from the investigators and from ClinicalTrials.gov (Figure 2; Figure 3).

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Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies
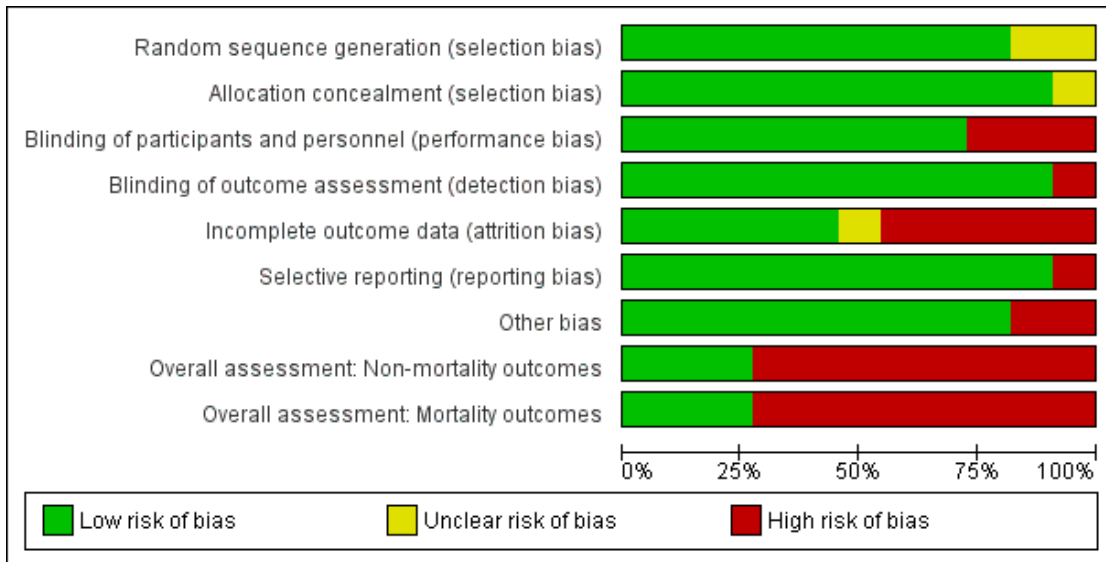
Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

Allocation

In nine of the 11 trials investigators generated the allocation sequence based on computer-generated random numbers (Bajaj 2013; Naderian 2017; Pockros 2009; Rahimi 2014; Rockey 2014; Shehata 2018; STOP-HE 2017; Uribe 1990; Ventura-Cots 2016). Two trials did not specify the method of sequence generation (Gonzalez 1994; Sushma 1992).

Four trials concealed the allocation of participants using sealed envelopes (Rahimi 2014; Shehata 2018; Sushma 1992; Ventura-Cots 2016). Four trials used central allocation (Bajaj 2013; Pockros 2009; Rockey 2014; Uribe 1990). One trial confirmed concealment of allocation, but not the specific method used (STOP-HE 2017). One trial utilized different personnel to ensure allocation was concealed (Naderian 2017). One study lacked information regarding the blinding of allocation (Gonzalez 1994).

We graded nine trials as having a low risk of selection bias (Bajaj 2013; Naderian 2017; Pockros 2009; Rahimi 2014; Rockey 2014; Shehata 2018; STOP-HE 2017; Uribe 1990; Ventura-Cots 2016) and two as having an unclear risk of selection bias (Gonzalez 1994; Sushma 1992).

Blinding

We graded eight trials as having a low risk of performance and detection bias (Bajaj 2013; Gonzalez 1994; Naderian 2017; Rockey 2014; STOP-HE 2017; Sushma 1992; Uribe 1990; Ventura-Cots 2016). We graded three trials as having a high risk of bias, as they were open-label trials without blinding (Pockros 2009; Rahimi 2014; Shehata 2018).

Incomplete outcome data

We graded five trials as having a low risk of attrition bias, as they used an intention-to-treat analysis, or included all participants in the analyses (Bajaj 2013; Shehata 2018; STOP-HE 2017; Uribe 1990; Ventura-Cots 2016). Five trials did not evaluate all randomised participants, and so we graded these as at high risk of attrition bias (Gonzalez 1994; Naderian 2017; Pockros 2009; Rahimi 2014; Sushma 1992). In one study the risk of attrition bias was unclear (Rockey 2014).

Selective reporting

Ten trials reported predefined, clinically relevant outcome measures, suggesting a low risk of selective reporting (Bajaj 2013; Gonzalez 1994; Naderian 2017; Pockros 2009; Rahimi 2014; Rockey 2014; Shehata 2018; Sushma 1992; Uribe 1990; Ventura-Cots 2016). We classified the remaining trial as having a high risk of reporting bias as it did not report the primary outcome of a change from baseline in hepatic encephalopathy stage (STOP-HE 2017).

Other potential sources of bias

We found no other potential sources of bias in nine trials (Bajaj 2013; Gonzalez 1994; Naderian 2017; Pockros 2009; Rockey 2014; Shehata 2018; Sushma 1992; Uribe 1990; Ventura-Cots 2016). We classified two trials as at high risk in respect of other potential bias: in one study, baseline blood urea nitrogen concentration was significantly higher in participants in the treatment group compared to the control group (Rahimi 2014), while in another trial we observed differences, some of them significant, in baseline characteristics, the severity of the underlying liver disease, the precipitant factors, and use of additional anti-encephalopathy treatments between participants recruited in the USA and elsewhere in the world (STOP-HE 2017).

Overall risk of bias

We classified eight trials at high risk of bias for all outcomes (Gonzalez 1994; Naderian 2017; Pockros 2009; Rahimi 2014; Rockey 2014; Shehata 2018; STOP-HE 2017; Sushma 1992), and three trials as at low risk of bias for all outcomes (Bajaj 2013; Uribe 1990; Ventura-Cots 2016).

Effects of interventions

See: **Summary of findings for the main comparison** Phamacotherapies that specifically target ammonia versus placebo or non-absorbable disaccharides for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis

Primary outcomes

All-cause mortality

We were able to gather mortality data from 11 trials involving 943 participants (Analysis 1.1). Our analyses found no beneficial or harmful effects of sodium benzoate versus non-absorbable disaccharides (RR 1.26, 95% CI 0.49 to 3.28; 101 participants; 2 trials; I^2 = 0%), glycerol phenylbutyrate versus placebo (RR 0.65, 95% CI 0.11 to 3.81; 178 participants; 1 trial), ornithine phenylacetate versus placebo (RR 0.73, 95% CI 0.35 to 1.51; 269 participants; 2 trials; I^2 = 0%), AST-120 versus lactulose (RR 1.05, 95% CI 0.59 to 1.85; 41 participants; 1 trial), or polyethylene glycol versus lactulose (RR 0.50, 95% CI 0.09 to 2.64; 190 participants; 3 trials; I^2 = 0%). There were no events in the trial of sodium benzoate versus placebo.

Hepatic encephalopathy

Seven trials involving 521 participants reported data on hepatic encephalopathy (Analysis 1.2). Our analyses showed a beneficial effect of glycerol phenylbutyrate versus placebo (RR 0.57, 95% CI 0.36 to 0.90; 178 participants; 1 trial; NNTB 6), and of polyethylene glycol versus lactulose (RR 0.19, 95% CI 0.08 to 0.44; 190 participants; 3 trials; I^2 = 0%; NNTB 4). We did not observe beneficial effects in the remaining three trials with extractable data viz. sodium benzoate versus non-absorbable disaccharides (RR 1.22, 95% CI 0.51 to 2.93; 74 participants; 1 trial); ornithine phenylacetate versus placebo (RR 2.71, 95% CI 0.12 to 62.70; 38 participants; 1 trial); or AST-120 versus lactulose (RR 1.05, 95% CI 0.59 to 1.85; 41 participants; 1 trial).

Serious adverse events

Ten trials, involving 790 participants, reported a total of 130 serious adverse events (Analysis 1.3). Our analyses found no beneficial or harmful effects of sodium benzoate versus non-absorbable disaccharides (RR 1.08, 95% CI 0.44 to 2.68; 101 participants; 2 trials), glycerol phenylbutyrate versus placebo (RR 1.63, 95% CI 0.85 to 3.13; 178 participants; 1 trial), ornithine phenylacetate versus placebo (RR 0.92, 95% CI 0.62 to 1.36; 264 participants; 2 trials; I^2 = 0%), or polyethylene glycol versus lactulose (RR 0.57, 95% CI 0.18 to 1.82; 190 participants; 3 trials; I^2 = 0%). There were no events in the trial evaluating sodium benzoate versus placebo or in the trial evaluating AST-120 versus lactulose.

Secondary outcomes

Non-serious adverse events

Eight trials, involving 782 participants, reported a total of 374 non-serious adverse events (Analysis 1.4). Our analyses found no beneficial or harmful effects of sodium benzoate versus non-absorbable disaccharides (RR 1.13, 95% CI 0.96 to 1.32; 182 participants; 2 trials; I^2 = 0%), glycerol phenylbutyrate versus placebo (RR 1.04, 95% CI 0.88 to 1.21; 178 participants; 1 trial), ornithine phenylacetate versus placebo (RR 1.08, 95% CI 0.78 to 1.51; 269 participants; 2 trials; I^2 = 11%), or polyethylene glycol versus non-absorbable disaccharides (RR 0.71, 95% CI 0.43 to 1.18; 137 participants; 2 trials). There were no events in the trial evaluating sodium benzoate versus placebo.

Health-related quality of life

One included trial with 48 participants (Pockros 2009), reported data on quality of life extracted from the sub-scores of the Hepatic Encephalopathy Scoring Algorithm (HESA: Table 2). Use of both AST-120 and lactulose resulted in improvement in anxiety and in memory for recent events; use of AST-120 was associated, in addition, with improvements in complex computations.

No other trials reported quality-of-life outcomes.

Blood ammonia

Nine trials, involving 733 participants, reported data on blood ammonia concentrations measured variously in venous and arterial blood (Table 3), and at various time points in the trial (Analysis 1.5). Our analyses showed a beneficial effect on blood ammonia concentration in trials of sodium benzoate versus placebo (MD −32.00 µg/dL, 95% CI −46.85 to −17.15; 16 participants; 1 trial), glycerol phenylbutyrate versus placebo (MD −12.00 µmol/L*week, 95% CI −23.37 to −0.63; 178 participants; 1 trial), ornithine phenylacetate versus placebo (MD −27.10 µmol/L, 95% CI −48.55 to −5.65; 231 participants; 1 trial), and AST-120 versus placebo (MD −22.00 µg/dL, 95% CI −26.75 to −17.25; 98 participants; 1 trial). However, there were no beneficial effects on blood ammonia concentration in the trials of sodium benzoate versus non-absorbable disaccharides (MD 9.80 µg/dL, 95% CI −0.48 to 20.08; 58 participants; 1 trial; and MD -14.94 µg/dL, 95% CI −71.32 to 41.44; 27 participants; 1 trial), AST-120 versus lactulose (MD 5.20 units not specified, 95% CI −2.75 to 13.15; 35 participants; 1 trial), or polyethylene glycol versus lactulose (MD −29.28 µmol/L, 95% CI −95.96 to 37.39; 90 participants; 2 trials).

'Summary of findings' tables

For all outcomes, we downgraded the certainty of the evidence by three levels to 'very low' as eight trials were at high risk of bias (one level) and the number of trials, participants, and events in each meta-analysis was small (two levels). See Summary of findings for the main comparison.

D I S C U S S I O N

Summary of main results

This systematic review included qualitative and quantitative data from 11 randomised clinical trials, involving 943 participants, treated with one of five drugs of interest. Although all five drugs specifically target ammonia, the ways in which they do so differ considerably. In consequence, we evaluated each separately and did not undertake any overall group analyses. In the primary analyses, we found evidence that glycerol phenylbutyrate had a beneficial effect on hepatic encephalopathy when compared to placebo (one trial) as did polyethylene glycol when compared to lactulose (three trials). We found no beneficial or harmful effects on hepatic encephalopathy in the other seven trials. None of these pharmacotherapies had a beneficial or harmful effect on the risk of mortality or the development of adverse events. The majority of

Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis (Review)

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these agents effectively lowered circulating ammonia concentrations when compared to placebo but not when compared to the non-absorbable disaccharides.

The certainty of the evidence was very low. This was because there were only three trials at low risk of bias and the number of trials, participants, and events in each analysis was small. Hence, no conclusions can be made with certainty regarding the clinical benefits and harms of these five pharmacotherapies.

Overall completeness and applicability of evidence

We included 11 randomised clinical trials with 943 participants with cirrhosis and a history or current evidence of hepatic encephalopathy. The trials were generally small, involving an average of 86 (range 18 to 231) people. Only five of the 11 trials conducted a sample size calculation for assessment of statistical power (Naderian 2017; Rahimi 2014; Rockey 2014; Shehata 2018; Ventura-Cots 2016). Of these, only two trials met the required sample size after withdrawal or loss of participants (Rahimi 2014; Shehata 2018). Thus, several of the trials are likely to be underpowered to detect a difference in the effectiveness and safety of the interventions. In addition, we classified eight of the 11 included trials at high risk of bias for all outcomes.

We evaluated five pharmacotherapies in this review. In most instances there was only one trial per comparison. Thus, three trials assessed sodium benzoate; one in a comparison with placebo (Gonzalez 1994), and two in comparison with non-absorbable disaccharides but with different agents (Sushma 1992; Uribe 1990). One trial assessed glycerol phenylbutyrate versus placebo (Rockey 2014). Two trials assessed ornithine phenylacetate against placebo (STOP-HE 2017; Ventura-Cots 2016). Two trials assessed AST-120, one in comparison with placebo (Bajaj 2013), and one in comparison with lactulose (Pockros 2009). Finally, three trials compared polyethylene glycol with lactulose (Naderian 2017; Rahimi 2014; Shehata 2018).

Overall, the included trials compared four of the five pharmacotherapies to placebo (Bajaj 2013; Gonzalez 1994; Rockey 2014; STOP-HE 2017; Ventura-Cots 2016); none of the trials undertook placebo-controlled trials of polyethylene glycol; this would be extremely difficult to do except in an open, likely unblinded, fashion. The trials compared three of the five pharmacotherapies to non-absorbable disaccharides (Naderian 2017; Pockros 2009; Rahimi 2014; Shehata 2018; Sushma 1992; Uribe 1990), the exceptions being glycerol phenylbutyrate and ornithine phenylacetate. None of the trials compared any of the five pharmacotherapies to other active agents, such as rifaximin or branched chain amino acids.

Four of the 11 trials were only published in abstract form and hence did not report all outcomes (Bajaj 2013; Gonzalez 1994; Pockros 2009; STOP-HE 2017). Although further information was obtainable from some trials, many authors did not, or could

not, provide us with the additional information we needed for our analyses. Data were also missing from some of the trials published as full papers; again some of these were retrievable from the trial authors but some were not. Thus, we could extract mortality data from all 11 trials but six of them reported no events. This limits the usefulness of these analyses, although we included three of the latter six trials in meta-analyses (Naderian 2017; Uribe 1990; Ventura-Cots 2016). We were able to retrieve data on hepatic encephalopathy from seven trials only, while data on serious adverse events were available from 10 trials, but with the same issue that we could not estimate the data in the four trials reporting no events. Differences in the way in which the trials utilized the drugs could confound the results. For example, in two of the three trials comparing polyethylene glycol to lactulose, participants were allowed to receive a single dose of lactulose prior to randomisation and after 24 hours of treatment regardless of their group allocation (Rahimi 2014), or were not given lactulose at all (Shehata 2018). However, the third trial gave lactulose to the participants allocated to polyethylene glycol in the same amount enterally or rectally as in the control group (Naderian 2017). Thus, two trials assessed polyethylene glycol as an alternative to lactulose (Rahimi 2014; Shehata 2018), whereas the other assessed it as an adjuvant (Naderian 2017).

The majority of trials used co-interventions alongside the study drug and, in the main, participants randomised to experimental or control groups had equal access to them. However, in the large, placebo-controlled trial of ornithine phenylacetate (STOP-HE 2017), 58% of participants were taking rifaximin, 5.2% were taking L-ornithine L-aspartate, and an unspecified proportion were taking lactulose, but no information was provided on the numbers of participants in the experimental and control groups involved. In addition, there were differences in the route of drug administration both between and within trials; for example, some trials administered study or control drugs or both by either enema or orally. Between trials, doses of the study or control substance or both also varied, which might have altered the effect size, particularly if the therapeutic effect is dose-dependent.

All participants included in our review had cirrhosis and a history of or current clinical evidence of hepatic encephalopathy. The majority of the included trials involved participants with an acute episode of hepatic encephalopathy (Gonzalez 1994; Naderian 2017; Rahimi 2014; Shehata 2018; STOP-HE 2017; Sushma 1992). Two trials involved participants with stable chronic hepatic encephalopathy (Pockros 2009; Uribe 1990), while one study involved participants with minimal and Grade 1 hepatic encephalopathy (Bajaj 2013). One study evaluated the primary prevention of hepatic encephalopathy following an upper gastrointestinal bleed (Ventura-Cots 2016), while one further trial evaluated the secondary prevention of hepatic encephalopathy in participants who had had at least two previous episodes of hepatic encephalopathy Grade 2 or greater in the previous six months (Rockey 2014). Thus, the included trials evaluated both the pre-

vention of hepatic encephalopathy and treatment of the various manifestations of the syndrome. However, no systematic evaluation of the use of the five pharmacotherapies across the spectrum of hepatic encephalopathy is possible based on the trials available to date. It would, therefore, be difficult to predict where these drugs might best fit into clinical practice.

Hepatic encephalopathy may also develop in people with non-cirrhotic portal hypertension and in people with acute liver failure but these people are encountered much less frequently than people with cirrhosis in clinical practice; these populations were not represented in the included trials. However, there is no reason why our results could not be extrapolated to people with hepatic encephalopathy associated with non-cirrhotic portal hypertension (e.g. portal vein block). The results may, on the other hand, not be directly applicable to people with fulminant hepatic failure.

Hepatic encephalopathy can often be precipitated by stressors such as infection, gastrointestinal bleeding, alcohol misuse or electrolyte disturbances. Therefore, it is important to be able to identify and treat these precipitating factors (AASLD/EASL 2014; Vilstrup 2014). The trials assessed in this review did not provide detailed information on possible precipitating events and the effects of the interventions designed to ameliorate them, nor did they evaluate the effects, if any, of the addition of pharmacotherapies that specifically target ammonia. It is, therefore, unclear whether these pharmacotherapies provide additional benefit in situations where hepatic encephalopathy is precipitated by a treatable event.

Hepatic encephalopathy imposes a significant burden on healthcare systems, and resource utilization associated with its management is increasing (Stepanova 2012). None of the randomised clinical trials included in this review conducted a detailed assessment of the costs associated with hospitalisation and treatment with pharmacotherapies that target ammonia. One study found that the cost of lactulose was 30 times the cost of sodium benzoate, although there is a possibility that this has changed, as the study was conducted over 15 years ago (Sushma 1992). Another study found that polyethylene glycol significantly reduced the length of hospital admission versus lactulose (Shehata 2018).

Whilst ammonia levels significantly decreased during use of most of the study drugs, the degree of hepatic encephalopathy, on the whole, did not significantly improve. This may reflect the fact that, while ammonia is known to play an important role in the pathogenesis of the syndrome, simply reducing circulating ammonia level may not be sufficient to reverse the complex cascade of events that contribute to the pathophysiology of this condition.

Quality of the evidence

The main reason for downgrading the certainty of the evidence in this review were incomplete outcome data (attrition bias), and the small number of trials giving rise to uncertainty.

We included randomised clinical trials published as full papers or abstracts and attempted to obtain additional information on

essential aspects of bias control from the authors of these works. We combined the individual bias domains into an overall assessment (hbg.cochrane.org/information-authors). We identified potential biases in all but three of the included trials (Bajaj 2013; Uribe 1990; Ventura-Cots 2016). We defined mortality, but not serious adverse events, as an outcome that is robust to performance and detection biases (Savović 2012a). This decision can be questioned, as lack of blinding is not likely to influence the assessment of serious adverse events such as variceal bleeding, hepatorenal syndrome, and liver failure. We classified all of the included trials but three (Bajaj 2013; Uribe 1990; Ventura-Cots 2016), as being at high risk in the overall assessments of mortality and non-mortality outcomes. Based on the assessment of incomplete outcome data (attrition bias), and due to the small number of trials giving rise to uncertainty, we classified the certainty of the evidence as very low for the assessment of all our outcomes.

Potential biases in the review process

We undertook the review based on current recommendations for bias control (hbg.cochrane.org/information-authors; Higgins 2017). We attempted to minimize possible selection bias (Page 2014), by using a comprehensive search strategy. We combined searches in electronic databases with hand searches of the biographies of identified trials, and the conference proceedings and abstract books from relevant national and international society meetings. We consider it unlikely that we failed to identify any published trials.

Two of the included trials, involving 216 participants, evaluated the prevention of hepatic encephalopathy while nine trials, involving 727 participants evaluated its treatment. We combined these trials in the analyses of the primary outcomes because they involved different agents and this may have introduced an element of bias.

Agreements and disagreements with other studies or reviews

This review is the first and largest identified systematic review of pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. It includes 11 randomised clinical trials involving five different specific pharmacotherapies and 943 participants. There are no other systematic reviews and meta-analyses evaluating these drugs with which to compare the findings of the present review. A number of general reviews of the management of hepatic encephalopathy have been published (Ahuja 2014; Bass 2007; Butterworth 2000; Jawaro 2016; Toris 2011), some of which look specifically at the drugs included in this review (Acharya 2018; De Las Heras 2017; Hadjihambi 2018; Jover-Cobos 2013; Kornerup 2018; Matoori 2015; Misel 2013; Rahimi 2016; Sturgeon 2014).

The EASL/AASLD Practice Guidelines state that further clinical reports are awaited on ornithine phenylacetate and that more trials are needed on glyceryl phenylbutyrate which, if they confirmed the original results, 'might lead to clinical recommendations' (AASLD/EASL 2014; Vilstrup 2014).

AUTHORS' CONCLUSIONS

Implications for practice

This review includes 11 randomised clinical trials evaluating the use of five pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis. The analyses found that these drugs have the potential to reduce blood ammonia concentrations, when compared to placebo, but the evidence was of low certainty. However, there is insufficient evidence to determine the effects of these pharmacotherapies on clinical outcomes and serious adverse events. Thus, further research is needed before these drugs can be fully evaluated and their place in clinical practice defined.

Implications for research

We used the EPICOT format (Brown 2006a), to define the implications for research.

Evidence (what is the current state of the evidence?). We included 11 trials involving 943 participants. We found evidence that sodium benzoate, glycerol phenylbutyrate, ornithine phenylacetate, and AST-120 effectively lower blood ammonia concentrations when compared to placebo and that polyethylene glycol lowered blood ammonia concentrations when compared to lactulose. However, there was little evidence that this ammonia-lowering effect translated into clinical benefit except that glycerol phenylbutyrate had a beneficial effect on hepatic encephalopathy when compared to placebo, and polyethylene glycol had a beneficial effect on hepatic encephalopathy when compared to lactulose. However, the certainty of the evidence was very low, and hence, we are very uncertain about these findings. Further high-quality randomised clinical trials are needed.

Participants (what is the population of interest?). We focused on people with cirrhosis and hepatic encephalopathy or people with cirrhosis who were at risk of developing hepatic encephalopathy. Because of the small number of randomised clinical trials available, we were not able to undertake subgroup analyses to determine differences in outcomes between trials looking at the prevention or treatment of hepatic encephalopathy, or determine if there were differences in outcomes by the degree of hepatic encephalopathy. Future trials should be designed to look for these potential differences. The effects of these drugs should also be assessed in people with hepatic encephalopathy associated with acute liver failure or with non-cirrhotic portal hypertension.

Interventions (what are the interventions of interest?): the interventions assessed are sodium benzoate, glycerol phenylbutyrate, ornithine phenylacetate, AST-120 (spherical carbon adsorbent), and polyethylene glycol. Although they all specifically target ammonia, they differ by mode of action, formulation, and route of administration. In some cases, the evidence for beneficial and harmful effects was based on only one trial and at most three. All the interventions considered in this review should be evaluated in further high-quality, randomised clinical trials.

Comparisons (what are the comparisons of interest?). The comparisons assessed in the trials in this review were a variety of placebo preparations and the non-absorbable disaccharides lactulose and lactitol. Future trials should include comparisons against placebo and no intervention, where considered feasible, and also against other agents thought to benefit people with hepatic encephalopathy, including non-absorbable disaccharides and non-absorbable antibiotics. Future trials should also evaluate the effect of co-interventions.

Outcomes (what are the outcomes of interest?). The primary outcomes included in this review - mortality, hepatic encephalopathy, and serious adverse events - should be included in any future trials. Health-related quality of life is also an important outcome, particularly in any future trials involving participants with minimal or chronic persistent hepatic encephalopathy. As these agents specifically target ammonia, blood ammonia concentrations will need to be monitored; the best outcome measure in relation to blood ammonia is the percentage change in concentration over trial baseline.

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REFERENCES

References to studies included in this review

Bajaj 2013 *{published data only (unpublished sought but not used)}*
Bajaj JS, Sheikh MY, Chojkier M, Balart L, Sherker AH,
Vemuru R, et al. AST-120 (spherical carbon adsorbent)
in covert hepatic encephalopathy: results of the Astute
trial. *Journal of Hepatology* 2013;**58**(Suppl 1):S84. DOI:
10.1016/S0168-8278(13)60192-0
* Bajaj JS, Sheikh MY, Chojkier M, Balart LA, Sherker
AH, Vemuru RP, et al. Su1685 AST-120 (spherical carbon
adsorbent) in covert hepatic encephalopathy: results of the
Astute trial. *Gastroenterology* 2013;**144**(5 (Suppl 1)):S997.

Gonzalez 1994 *{published data only (unpublished sought but not
used)}*
Gonzalez A, Neri M, Campollo O, Amacio O. Treatment
of acute portal systemic encephalopathy (PSE) grades III
and IV with sodium benzoate and lactose. *Hepatology
(Baltimore, Md.)* 1994;**19**(4 Suppl):67I.

Naderian 2017 *{published and unpublished data}*
Naderian M, Heshmatollah A, Saeedi M, Sohrabpour A.
Polyethylene glycol and lactulose alone in the treatment of
hepatic encephalopathy in patients with cirrhosis: a non-
inferiority randomised control trial. *Middle East Journal of
DIgestive Diseases* 2017;**9**(1):12–9. PUBMED: 28316761]

Pockros 2009 *{published data only (unpublished sought but not used)}*
Pockros P, Hassanein T, Vierling J, Heuman D, Hillebrand
D, Chojkier M. Phase 2, multicenter, randomised study
of AST-120 (spherical carbon adsorbent) vs. lactulose in
the treatment of low-grade hepatic encephalopathy (HE).
Journal of Hepatology 2009; Vol. 50, issue Suppl 1:S43.
CN–00715816]

Rahimi 2014 *{published data only}*
* Rahimi R, Singal A, Cuthbert J, Rockey D. Lactulose vs
polyethylene glycol 3350-electrolyte solution for treatment
of overt hepatic encephalopathy: the HELP randomised
clinical trial. *Journal of the American Medical Association
Internal Medicine* 2014;**174**(11):1727–33. PUBMED:
25243839]
Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. A
randomised trial of polyethylene glycol 3350-electrolyte
solution (PEG) and lactulose for patients hospitalized with
acute hepatic encephalopathy. *Hepatology (Baltimore, Md.)*
2012;**56**(Suppl):915A–6A.

Rockey 2014 *{published data only (unpublished sought but not used)}*
Jurek M, Mokhtarani M, Vierling J, Coakley D, Ganju J,
Rowell R, et al. Variation in liver biochemistries in patients
with decompensated cirrhosis: implications for assessing
drug-induced liver injury in clinical trials. *Pharmaceutical
Medicine* 2016;**30**(2):95–101.
* Rockey DC, Vierling JM, Mantry P, Ghabril M, Brown
RS Jr, Alexeeva O, et al. Randomized, double-blind,
controlled study of glycerol phenylbutyrate in hepatic
encephalopathy. *Hepatology (Baltimore, Md.)* 2014;**59**(3):
1073–83. PUBMED: 23847109]

Shehata 2018 *{published data only}*
Shehata HH, Elfert AA, Abdin AA, Soliman SM, Elkhouly
RA, Hawah NI, et al. Randomized controlled trial of
polyethylene glycol versus lactulose for the treatment
of overt hepatic encephalopathy. *European Journal of
Gastroenterology & Hepatology* 2018;**30**(12):1476–81. DOI:
10.1097/MEG.0000000000001267

STOP-HE 2017 *{published and unpublished data}*
Rahimi RS, Safadi R, Thabut D, Bajaj JS, Bhamidimarri
KR, Pyrsopoulos NT, et al. STOP-HE: a randomised,
double-blind, placebo-controlled study of OCR-002
in patients with hepatic encephalopathy. *Hepatology
(Baltimore, Md.)* 2017;**66**(Suppl 1):276A.
Safadi R, Rahimi RS, DiLiberti CE, Wang L, Pyrsopoulos
NT, Pothoff AP, et al. OCR-002 (ornithine phenylacetate)
is a potent ammonia scavenger as demonstrated in phase 2b
STOP-HE study. *Hepatology (Baltimore, Md.)* 2017;**66**
(Suppl 1):126A.
Thabut D, Stadlbauer V, Bhamidimarri KR, Pothoff A,
Bukofzer S, on behalf of the STOP-HE study group.
Geographic differences for patients enrolled in STOP-
HE: a randomised, phase 2 study of OCR-002 for hepatic
encephalopathy. *Hepatology (Baltimore, Md.)* 2017;**66**
(Suppl 1):274A.

Sushma 1992 *{published data only (unpublished sought but not used)}*
Sushma S, Dasarathy S, Tandon RK, Jain S, Gupta S,
Bhist MS. Sodium benzoate in the treatment of acute
hepatic encephalopathy: a double-blind randomised
trial. *Hepatology (Baltimore, Md.)* 1992;**16**(1):138–44.
PUBMED: 1618465]

Uribe 1990 *{published data only}*
Uribe M, Bosques F, Marín E, Cervera E, Gil S, Poo JL,
et al. Sodium benzoate in portalsystemic encephalopathy

induced blood ammonia normalization and clinical improvement. Interim report of a double blind multicenter trial [Derivacion metabolica del amonio plasmatico con benzoato de sodio, como metodo de tratamiento en pacientes con cirrosis y encefalopatia portosistemica. Informe interino de un estudio multicentrico, doble ciego]. *Revista de Investigación Clínica* 1990;**42**(Suppl):149–54. PUBMED: 19256155]

Ventura-Cots 2016 *{published and unpublished data}*
Ventura-Cots M, Arranz JA, Simón-Talero M, Torrens M, Blanco A, Riudor E, et al. Safety of ornithine phenylacetate in cirrhotic decompensated patients: an open-label, dose-escalating, single-cohort study. *Journal of Clinical Gastroenterology* 2013;**47**(10):881–7. PUBMED: 23751856]
* Ventura-Cots M, Concepción M, Arranz JA, Simón-Talero M, Torrens M, Blanco-Grau A, et al. Impact of ornithine phenylacetate (OCR-002) in lowering plasma ammonia after upper gastrointestinal bleeding in cirrhotic patients. *Therapeutic Advances in Gastroenterology* 2016;**9**(6):823–35. PUBMED: 27803737]

References to studies excluded from this review

Campollo 1992 *{published data only}*
Campollo O, Gil S, Olvera G, Poo JL, Uribe M. Efficacy and safety of sodium benzoate for the long-term treatment of chronic hyperammonemic hepatic encephalopathy. *Hepatology (Baltimore, Md.)* 1992;**16**(Suppl 1):248A.

Ghabril 2013 *{published data only}*
Ghabril M, Zupanets I, Vierling J, Mantry P, Rockey D, Wolf D, et al. Glycerol phenylbutyrate in patients with cirrhosis and episodic hepatic encephalopathy: a pilot study of safety and effect on venous ammonia concentration. *Clinical Pharmacology in Drug Development* 2013;**2**(3):278–84. PUBMED: 27121790]

Mendenhall 1986 *{published data only}*
Mendenhall CL, Rouster S, Marshall L, Weesner R. A new therapy for portal systemic encephalopathy. *American Journal of Gastroenterology* 1986;**81**(7):540–3. PUBMED: 3717115]

Panella 1993 *{published data only}*
Panella C, Guglielmi FW, Mastronuzzi T, Contento F, Siciliano N, Francavilla A. Oral Na-benzoate in the treatment of chronic hepatic encephalopathy. *Italian Journal of Gastroenterology* 1993;**25**:228.
Panella C, Guglielmi FW, Mastronuzzi T, Contento F, Siciliano N, Francavilla A. Oral sodium benzoate in the treatment of chronic hepatic encephalopathy. *Gut* 1993;**34**(Suppl 3):S43.

Weiss 2018 *{published data only}*
Tripon S, Mallet M, Lodey M, Guiller E, Rudler M, Mouri S, et al. Sodium phenylbutyrate administration to avoid neurological worsening in cirrhotic patients with hepatic

encephalopathy admitted in ICU. *Journal of Hepatology* 2016;**64**(2 Suppl):S288.
* Weiss N, Tripon S, Lodey M, Guiller E, Junot H, Monneret D, et al. Treating hepatic encephalopathy in cirrhotic patients admitted to ICU with sodium phenylbutyrate: a preliminary study. *Fundamental & Clinical Pharmacology* 2018;**32**(2):206–8.

References to ongoing studies

NCT00558038 *{published data only}*
NCT00558038. Safety and efficacy of AST-120 compared to lactulose in patients with hepatic encephalopathy (AST015). clinicaltrials.gov/ct2/show/NCT00558038 (first posted 14 November 2007).

NCT03448770 *{unpublished data only}*
NCT03448770. To compare efficacy and safety of lactulose versus polyethylene glycol for treatment of overt hepatic encephalopathy in cirrhotics: a randomised controlled trial. clinicaltrials.gov/ct2/show/nct03448770 (first posted 28 February 2018).

Additional references

AASLD/EASL 2014
American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *Journal of Hepatology* 2014;**61**(3):642–59.

Acharya 2018
Acharya C, Bajaj J. Current management of hepatic encephalopathy. *American Journal of Gastroenterology* 2018;**113**(11):1600–12.

Ahuja 2014
Ahuja N, Ally W, Caldwell S. Direct acting inhibitors of ammoniagenesis: a role in post-TIPS encephalopathy?. *Annals of Hepatology* 2014;**13**(2):179–86.

Allampati 2016
Allampati S, Duarte-Rojo A, Thacker L, Patidar K, White M, Klair J, et al. Diagnosis of minimal hepatic encephalopathy using strop EncephalApp: a multicentre US-based, norm-based study. *American Journal of Gastroenterology* 2016;**111**(1):78–86. [PUBMED: 26644276]

Bajaj 2008
Bajaj JS, Hafeezullah M, Franco J, Varma RR, Hoffmann RG, Knox JF, et al. Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. *Gastroenterology* 2008;**135**(5):1591–600. [PUBMED: 18723018]

Bajaj 2009
Bajaj JS, Wade JB, Sanyal AJ. Spectrum of neurocognitive impairment in cirrhosis: implications for the assessment of hepatic encephalopathy. *Hepatology (Baltimore, Md.)* 2009;**50**(6):2014–21. DOI: 10.1002/hep.23216; PUBMED: 19787808

Bajaj 2010
Bajaj JS, Schubert CM, Heuman DM, Wade JB, Gibson DP, Topaz A, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology* 2010;**138**(7):2332–40. [PUBMED: 20178797]

Bajaj 2011a
Bajaj JS, Cordoba J, Mullen KD, Amodio P, Shawcross DL, Butterworth RF, et al. Review article: the design of clinical trials in hepatic encephalopathy - an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. *Alimentary Pharmacology & Therapeutics* 2011;**33**(7):739–47. [PUBMED: 21306407]

Bajaj 2011b
Bajaj JS, Wade JB, Gibson DP, Heuman DM, Thacker LR, Sterling RK, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *American Journal of Gastroenterology* 2011;**106**(9):1646–53. [PUBMED: 21556040]

Bass 2007
Bass N. Review article: the current pharmacological therapies for hepatic encephalopathy. *Alimentary Pharmacology & Therapeutics* 2007;**25**(S1):23–31.

Berry 2014
Berry SA, Lichter-Konecki U, Diaz GA, McCandless SE, Rhead W, Smith W, et al. Glycerol phenylbutyrate treatment in children with urea cycle disorders: pooled analysis of short and long-term ammonia control and outcomes. *Molecular Genetics and Metabolism* 2014;**112**(1):17–24. [PUBMED: 24630270]

Blanco Vela 2011
Blanco Vela CI, Bosques Padilla FJ. Determination of ammonia concentrations in cirrhosis patients - still confusing after all these years?. *Annals of Hepatology* 2011;**10**(Suppl 2):S60–5. [PUBMED: 22228884]

Bosoi 2011
Bosoi CR, Parent-Robitaille C, Anderson K, Tremblay M, Rose CF. AST-120 (spherical carbon adsorbent) lowers ammonia levels and attenuates brain edema in bile duct-ligated rats. *Hepatology (Baltimore, Md.)* 2011;**53**(6):1995–2002. [PUBMED: 21384402]

Brown 2006a
Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. *BMJ (Clinical Research Ed.)* 2006;**333**(7572):804–6. [PUBMED: 17038740]

Bustamante 1999
Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I I, Reggiardo V, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *Journal of Hepatology* 1999;**30**(5):890–5. [PUBMED: 10365817]

Butterworth 2000
Butterworth R. Complications of cirrhosis III. Hepatic encephalopathy. *Journal of Hepatology* 2000;**32**(Suppl 1):171–80.

Butterworth 2013
Butterworth RF. The liver-brain axis in liver failure: neuroinflammation and encephalopathy. *Nature Reviews. Gastroenterology & Hepatology* 2013;**10**(9):522–8. [PUBMED: 23817325]

Cadranel 2001
Cadranel JF, Lebiez E, Di Martino V, Bernard B, El Koury S, Tourbah A, et al. Focal neurological signs in hepatic encephalopathy in cirrhotic patients: an underestimated entity?. *American Journal of Gastroenterology* 2001;**96**(2):515–8. [PUBMED: 11232699]

Chu 1997
Chu NS, Yang SS, Liaw YF. Evoked potentials in liver diseases. *Journal of Gastroenterology and Hepatology* 1997;**12**(Suppl):S288–93. [PUBMED: 9407349]

Conn 1977
Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology* 1977;**72**(4 Pt 1):573–83. [PUBMED: 14049]

De Jongh 1992
De Jongh FE, Janssen HL, De Man RA, Hop WC, Schalm SW, Van Blankenstein M. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. *Gastroenterology* 1992;**103**(5):1630–5. [PUBMED: 1426884]

De Las Heras 2017
De Las Heras J, Aldámiz-Echevarría L, Martínez-Chantar ML, Delgado T. An update on the use of benzoate, phenylacetate and phenylbutyrate ammonia scavengers for interrogating and modifying liver nitrogen metabolism and its implications in urea cycle disorders and liver disease. *Expert Opinion on Drug Metabolism & Toxicology* 2017;**13**(4):439–48.

Deeks 2017
Deeks JJ, Higgins JP, Altman DG (editors) on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Dhiman 1995
Dhiman RK, Saraswat VA, Verma M, Naik SR. Figure connection test: a universal test for assessment of mental state. *Journal of Gastroenterology and Hepatology* 1995;**10**(1):14–23. [PUBMED: 7620102]

D'Amico 1986
D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Digestive Diseases and Sciences* 1986;**31**(5):468–75. [PUBMED: 3009109]

D'Amico 2006
D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic

review of 118 studies. *Journal of Hepatology* 2006;**44**: 217–31.

Efrati 2000

Efrati C, Masini A, Merli M, Valeriano V, Riggio O. Effect of sodium benzoate on blood ammonia response to oral glutamine challenge in cirrhotic patients: a note of caution. *American Journal of Gastroenterology* 2000;**95**(12):3574–8. [PUBMED: 11151894]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629–34.

Ferenci 2002

Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology (Baltimore, Md.)* 2002;**35**(3): 716–21. [PUBMED: 11870389]

Gluud 2016

Gluud LL, Vilstrup H, Morgan MY. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. *Cochrane Database Systematic Review* 2016;**5**:CD003044. DOI: 10.1002/14651858.CD003044.pub4; PUBMED: 27153247

Goh 2018

Goh ET, Stokes CS, Sidhu SS, Vilstrup H, Gluud LL, Morgan MY. L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. *Cochrane Database of Systematic Reviews* 2018, Issue 5. DOI: 10.1002/14651858.CD012410.pub2

GradePro 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro. Version accessed 16 August 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Groeneweg 1998

Groeneweg M, Quero JC, De Bruijn I, Hartmann IJ, Essink-bot ML, Hop WC, et al. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology (Baltimore, Md.)* 1998;**28**(1):45–9. [PUBMED: 9657095]

Guérit 2009

Guérit JM, Amantini A, Fischer C, Kaplan PW, Mecarelli O, Schnitzler A, et al. Neurophysiological investigations of hepatic encephalopathy: ISHEN practice guidelines. *Liver International* 2009;**29**(6):789–96. [PUBMED: 19638107]

Hadjihambi 2018

Hadjihambi A, Arias N, Sheikh M, Jalan R. Hepatic encephalopathy: a critical current review. *Hepatology International* 2018;**12**(Suppl 1):135–47.

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20): 3443–57. [PUBMED: 16345038]

Hassanein 2008

Hassanein TI, Hilsabeck RC, Perry W. Introduction to the Hepatic Encephalopathy Scoring Algorithm (HESA). *Digestive Diseases and Sciences* 2008;**53**(2):529–38. DOI: 10.1007/s10620-007-9895-0; PUBMED: 17710551

Haussinger 2000

Haussinger D, Kircheis G, Fischer R, Schliess F, vom Dahl S. Hepatic encephalopathy in chronic liver disease: a clinical manifestation of astrocyte swelling and low-grade cerebral edema?. *Journal of Hepatology* 2000;**32**(6):1035–8. [PUBMED: 10898326]

Higgins 2008

Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clinical Trials* 2008;**5**(3):225–39.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2017

Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017 Available from: www.training.cochrane.org/handbook.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. *International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice CFR & ICH Guidelines*. Vol. **1**, Philadelphia (PA): Barnett International/PAREXEL, 1997.

Jackson 2016

Jackson CD, Gram M, Halliday E, Olesen SS, Sandberg TH, Drewes AM, et al. New spectral thresholds improve the utility of the electroencephalogram for the diagnosis of hepatic encephalopathy. *Clinical Neurophysiology* 2016; **127**(8):2933–41. DOI: 10.1016/j.clinph.2016.03.027; PUBMED: 27236607

Jalan 2007

Jalan R, Wright G, Davies NA, Hodges SJ. L-Ornithine phenylacetate (OP): a novel treatment for hyperammonemia and hepatic encephalopathy. *Medical Hypotheses* 2007;**69** (5):1064–9. [PUBMED: 17467190]

Jawaro 2016

Jawaro T, Yang A, Dixit D, Bridgeman M. Management of hepatic encephalopathy. *Annals of Pharmacology* 2016;**50** (7):569–77.

Jepsen 2010

Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. The clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology (Baltimore, Md.)* 2010;**51**(5):1675–82. DOI: 10.1002/hep.23500; PUBMED: 20186844

Jover-Cobos 2013

Jover-Cobos M, Noiret L, Sharifi Y, Jalan R. Ornithine phenylacetate revisited. *Metabolic Brain Disease* 2013;**28**(2): 327–31. [PUBMED: 23456516]

Kircheis 2002

Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Haussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. *Hepatology (Baltimore, Md.)* 2002;**35**(2):357–66. [PUBMED: 11826409]

Kircheis 2009

Kircheis G, Knoche A, Hilger N, Manhart F, Schnitzler A, Schulze H, et al. Hepatic encephalopathy and fitness to drive. *Gastroenterology* 2009;**137**(5):1706–15. [PUBMED: 19686744]

Kornerup 2018

Kornerup L, Gluud L, Vilstrup H, Dam G. Update on the therapeutic management of hepatic encephalopathy. *Current Gastroenterology Reports* 2018;**20**(5):20–1.

Lauridsen 2011

Lauridsen MM, Jepsen P, Vilstrup H. Critical flicker frequency and continuous reaction times for the diagnosis of minimal hepatic encephalopathy: a comparative study of 154 patients with liver disease. *Metabolic Brain Disease* 2011;**26**(2):135–9. [PUBMED: 21484318]

Lee 2010

Lee B, Rhead W, Diaz GA, Scharschmidt BF, Mian A, Shchelochkov O, et al. Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. *Molecular Genetics and Metabolism* 2010;**100**(3):221–8. [PUBMED: 20382058]

Lockwood 2004

Lockwood AH. Blood ammonia levels and hepatic encephalopathy. *Metabolic Brain Disease* 2004;**19**(3-4): 345–9. [PUBMED: 15554426]

Mardini 2008

Mardini H, Saxby BK, Record CO. Computerized psychometric testing in minimal encephalopathy and modulation by nitrogen challenge and liver transplant. *Gastroenterology* 2008;**135**(5):1582–90. DOI: 10.1053/ j.gastro.2008.06.043; PUBMED: 18647604

Matoori 2015

Matoori S, Leroux JC. Recent advances in the treatment of hyperammonemia. *Advanced Drug Delivery Reviews* 2015; **90**(1):55–68.

McGuire 2010

McGuire BM, Zupanets IA, Lowe ME, Xiao X, Syplyviy VA, Monteleone J, et al. Pharmacology and safety of glycerol phenylbutyrate in healthy adults and adults with cirrhosis. *Hepatology (Baltimore, Md.)* 2010;**51**(6): 2077–85. [PUBMED: 20512995]

MECIR 2018

Higgins JP, Lasserson T, Chandler J, Tovey D, Churchill R. Methodological expectations of Cochrane intervention reviews - Version 1.07. community.cochrane.org/mecir-manual 2018 (accessed 5 March 2019).

Misel 2013

Misel ML, Gish RG, Patton H, Mendler M. Sodium benzoate for treatment of hepatic encephalopathy. *Gastroenterology & Hepatology* 2013;**9**(4):219–27. [PUBMED: 24711766]

Montagnese 2004

Montagnese S, Amodio P, Morgan MY. Methods for diagnosing hepatic encephalopathy in patients with cirrhosis: a multidimensional approach. *Metabolic Brain Disease* 2004;**19**(3-4):281–312. [PUBMED: 15554423]

Montagnese 2014

Montagnese S, Balistreri E, Schiff S, De Rui M, Angeli P, Zanus G, et al. Covert hepatic encephalopathy: agreement and predictive validity of different indices. *World Journal of Gastroenterology* 2014;**20**(42):15756–62. DOI: 10.3748/ wjg.v20.i42.15756; PMCID: PMC4229541; PUBMED: 25400460

Morgan 2018

Morgan MY. Hepatic encephalopathy. In: Dooley JS, Lok ASF, Garcia-Tsao G, Pinzani M editor(s). *Sherlock's Diseases of the Liver and Biliary System*. 13th Edition. London: Wiley-Blackwell, 2018:Chapter 10: pp 151-80. [ASIN: 1119237548; ISBN–13: 978–1119237549]

O'Carroll 1991

O'Carroll RE, Hayes PC, Ebmeier KP, Dougall N, Murray C, Best JJ, et al. Regional cerebral blood flow and cognitive function in patients with chronic liver disease. *Lancet* 1991; **337**(8752):1250–3. [PUBMED: 1674063]

Olesen 2016

Olesen SS, Gram M, Jackson CD, Halliday E, Sandberg TH, Drewes AM, et al. Electroencephalogram variability in patients with cirrhosis associates with the presence and severity of hepatic encephalopathy. *Journal of Hepatology* 2016;**65**(3):517–23. DOI: 10.1016/j.jhep.2016.05.004; PUBMED: 27184531

Ortiz 2007

Ortiz M, Córdoba J, Doval E, Jacas C, Pujadas F, Esteban R, et al. Development of a clinical hepatic encephalopathy staging scale. *Alimentary Pharmacology & Therapeutics* 2007; **26**(6):859–67. DOI: 10.1111/j.1365-2036.2007.03394.x; PUBMED: 17767470

Page 2014

Page MJ, McKenzie JE, Kirkham J, Dwan K, Kramer S, Green S, et al. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. *Cochrane Database of Systematic Reviews* 2014, Issue 10. DOI: 10.1002/14651858.MR000035.pub2; MR000035

Pantham 2017

Pantham G, Post A, Venkat D, Einstadter D, Mullen KD. A new look at precipitants of overt hepatic encephalopathy in cirrhosis. *Digestive Diseases and Sciences* 2017;**62**(8): 2166–73. DOI: 10.1007/s10620-017-4630-y; PUBMED: 28560484

Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis (Review)

34

Parsons-Smith 1957

Parsons-Smith BG, Summerskill WH, Dawson AM, Sherlock S. The electroencephalograph in liver disease. *Lancet* 1957;**270**(7001):867–71. [PUBMED: 13482229]

Poodad 2007

Poodad FF. Review article: the burden of hepatic encephalopathy. *Alimentary Pharmacology & Therapeutics* 2007;**25**(Suppl 1):3–9.

Rahimi 2016

Rahimi RS, Rockey DC. Hepatic encephalopathy: pharmacological therapies targeting ammonia. *Seminars in Liver Disease* 2016;**36**(1):48–55. [PUBMED: 26870932]

Randolph 1998

Randolph C. *The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)*. San Antonio: The Psychological Corporation, 1998.

Randolph 2009

Randolph C, Hilsabeck R, Kato A, Kharbanda P, Li YY, Mapelli D, et al. Neuropsychological assessment of hepatic encephalopathy: ISHEN practice guidelines. *Liver International* 2009;**29**(5):629–35. [PUBMED: 19302444]

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roman 2011

Roman E, Córdoba J, Torrens M, Torras X, Villanueva C, Vargas V, et al. Minimal hepatic encephalopathy is associated with falls. *American Journal of Gastroenterology* 2011;**106**(3):476–82.

Rose 2012

Rose CF. Ammonia-lowering strategies for the treatment of hepatic encephalopathy. *Clinical Pharmacology and Therapeutics* 2012;**92**(3):321–31. [PUBMED: 22871998]

Royle 2003

Royle P, Milne R. Literature searching for randomised controlled trials used in Cochrane Reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(1):591–603.

Saunders 1981

Saunders JB, Walters JR, Davies AP, Paton A. A 20-year prospective study of cirrhosis. *BMJ (Clinical Research Ed.)* 1981;**282**(6260):263–6. [PUBMED: 6779978]

Savović 2012a

Savović J, Jones H, Altman D, Harris R, Juni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment* 2012;**16**(35):1–82. [PUBMED: 22989478]

Savović 2012b

Savović J, Jones HE, Altman DG, Harris RJ, Juni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised, controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429–38. [PUBMED: 22945832]

Schomerus 1981

Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Dölle W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. *Digestive Diseases and Sciences* 1981;**26**(7):522–30. [PUBMED: 7249898]

Schomerus 1998

Schomerus H, Hamster W. Neuropsychological aspects of portal-systemic encephalopathy. *Metabolic Brain Disease* 1998;**13**(4):361–77. [PUBMED: 10206827]

Schünemann 2013

Schünemann H, Broż ek J, Guyatt G, Oxman A, editor (s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. gdt.gradepro.org/app/handbook/handbook.html 2013 (accessed 24 January 2019).

Sharma 2010

Sharma P, Sharma BC, Sarin SK. Predictors of non response to lactulose in patients with cirrhosis and hepatic encephalopathy. *European Journal of Gastroenterology & Hepatology* 2010;**22**(5):526–31. [PUBMED: 20009938]

Sotil 2009

Sotil EU, Gottstein J, Ayala E, Randolph C, Blei AT. Impact of preoperative overt hepatic encephalopathy on neurocognitive function after liver transplantation. *Liver Transplantation* 2009;**15**(2):184–92.

Stata 2015 [Computer program]

Stata Corp. Stata: Release 14. Texas, USA: Stata Corp, 2015.

Stepanova 2012

Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. *Clinical Gastroenterology and Hepatology* 2012;**10**(9): 1034–41.

Stewart 2007

Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. *Liver Transplantation* 2007;**13**(10): 1366–71.

Sturgeon 2014

Sturgeon J, Shawcross D. Recent insights into the pathogenesis of hepatic encephalopathy and treatments. *Expert Review of Gastroenterology & Hepatology* 2014;**8**(1): 83–100.

Taylor-Robinson 1994

Taylor-Robinson SD, Sargentoni J, Marcus CD, Morgan MY, Bryant DJ. Regional variations in cerebral proton spectroscopy in patients with chronic hepatic encephalopathy. *Metabolic Brain Disease* 1994;**9**(4):347–59. [PUBMED: 7898401]

Teasdale 1974
Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;**304**(7872): 81–4. [PUBMED: 4136544]

Toris 2011
Toris G, Bikis C, Tsourouflis G, Theocharis S. Hepatic encephalopathy: an updated approach from pathogenesis to treatment. *Medical Science Monitor* 2011;**17**(2):RA53–63. [PUBMED: 21278704]

Victor 1965
Victor M, Adams RD, Cole M. The acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. *Medicine* 1965;**44**(5):345–96. [PUBMED: 5318075]

Vilstrup 2014
Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology (Baltimore, Md.)* 2014;**60**(2):715–35. [PUBMED: 25042402]

Weissenborn 1998
Weissenborn K. Diagnosis of encephalopathy. *Digestion* 1998;**59**(Suppl 2):22–4.

Weissenborn 2001
Weissenborn K, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. *Journal of Hepatology* 2001;**34**(5):768–73. [PUBMED: 11434627]

Wetterslev 2008
Wetterslev J, Thorlund K, Brok J, Gluud C. Trial Sequential Analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64–75.

Wright 2011
Wright G, Noiret L, Olde Damink SW, Jalan R. Interorgan ammonia metabolism in liver failure: the basis of current and future therapies. *Liver International* 2011;**31**(2): 163–75. DOI: 10.1111/j.1478-3231.2010.02302.x; PUBMED: 20673233

Zacharias 2017
Zacharias HD, Jackson CD, Morgan MY, Olesen SS . Alimentary Pharmacology, Therapeutics. Stepwise diagnosis in covert hepatic encephalopathy - critical flicker frequency and MELD-score as a first-step approach. Replication and pitfalls. *Alimentary Pharmacology & Therapeutics* 2017;**45**(1):187–9. DOI: 10.1111/apt.13830; PUBMED: 27910151

Zipprich 2012
Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. *Liver International* 2012;**32**(9):1407–14. [PUBMED: 22679906]

References to other published versions of this review

Zacharias 2016
Zacharias HD, Zacharias AP, Oliveira Ferreira A, Morgan MY, Gluud LL. Ammonia scavenging agents for people with cirrhosis and hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2016, Issue 8. DOI: 10.1002/14651858.CD012334

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[author-defined order]*

Gonzalez 1994

Methods	**Sodium benzoate:** single-centre, double-blind, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis with acute Grade 3 or 4 hepatic encephalopathy (n = 18); 2 participants were excluded shortly after inclusion because of gastrointestinal bleeding **Age:** not reported **Proportion of men:** not reported **Aetiology of the liver disease:** not reported **MELD score:** not reported
Interventions	**Intervention comparison:** sodium benzoate vs placebo **Sodium benzoate:** 7.2 g/24 h administered orally or via nasogastric tube (n = 7) **Placebo:** (not detailed) administered orally or via nasogastric tube (n = 9) **Duration of treatment:** 7 days **Co-intervention:** participants in both groups received lactose enemata (200 g/L) thrice-daily
Outcomes	**Neurocognitive assessment:** Modified PSE Index comprising: • mental status (West Haven Criteria) • asterixis • Number Connection Test A • venous blood ammonia **Others:** • time to awakening
Inclusion period	Not reported
Country of origin	Mexico
Outcomes included in meta-analyses	• Mortality • Adverse events • Venous blood ammonia
Notes	**Publication status:** abstract • The authors reported that the characteristics of the treatment and control groups were comparable • The trial describes the effects of the interventions on hepatic encephalopathy based on change over the trial period in mental status (West Haven Criteria) and the PSE Index. • The authors give the impression that none of the included participants died, although this was no explicitly conveyed. **Funding:**

	• No information provided	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel using a placebo
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Blinding of outcome assessment using a placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	Two participants were excluded due to gastrointestinal bleeding. The allocation group of these participants was not reported
Selective reporting (reporting bias)	Low risk	The trial reported clinically relevant outcomes. We did not have access to the trial protocol
Other bias	Low risk	None identified
Overall assessment Non-mortality outcomes	High risk	
Overall assessment Mortality outcomes	High risk	

Sushma 1992

Methods	**Sodium benzoate:** single-centre, double-blind, randomised clinical trial
Participants	**Included participants:** overt hepatic encephalopathy, Grade 2-4, associated with cirrhosis or creation of a surgical portal-systemic anastomosis with evidence of fibrosis (n = 74) **Age** (mean ± SD): • sodium benzoate group 35.6 ± 18.4 years • lactulose group 37.9 ± 12.8 years. **Proportion of men:** • sodium benzoate group 79%

	• lactulose group 72%. **Aetiology of liver disease** (sodium benzoate: lactulose group): • post-hepatitis 66%: 75% • alcohol 26%: 22% **MELD score:** not reported
Interventions	**Intervention comparison:** sodium benzoate vs lactulose **Sodium benzoate:** 5 g/30 mL tap water, given orally or via nasogastric tube twice daily (n = 38); standard dose 10 g/day for 7.9 ± 6.4 days **Lactulose:** 30 mL/8 h administered orally or by nasogastric tube; dose adjusted to achieve 3 semi-soft stools daily (n = 36); mean dose 66.8 ± 24.8 mL/day for 8.8 ± 7.1 days **Duration of treatment:** until complete recovery - maximum follow-up 42 days **Co-intervention:** standard treatment was continued in both groups and included twice-daily bowel washes with tap water, maintenance of fluid and electrolyte levels, restriction of oral intake of proteins to 20 g/day in participants in whom oral intake was possible; antibiotics were prescribed to treat infections in 7 participants receiving sodium benzoate and in 1 participant receiving lactulose
Outcomes	**Neuropsychiatric assessment** PSE Sum and Index comprising: • mental status (West Haven Criteria) • asterixis • Number Connection Test A • arterial blood ammonia • electroencephalography Additional psychometric tests including: • 5-pointed star construction • serial-7 subtraction • backward counting tests Visual, auditory and somatosensory evoked potentials **Others:** • time elapsed before response
Inclusion period	January 1990-June 1991
Country of origin	India
Outcomes included in meta-analyses	• Mortality • Hepatic encephalopathy • Serious adverse events • Non-serious adverse events • Blood ammonia
Notes	**Publication status:** full paper • Separate results were not provided for the 2 participants who developed hepatic encephalopathy following portal-systemic shunt surgery with underlying hepatic fibrosis. They are included in the overall analyses. • Therapeutic success was defined as a sustained improvement of one grade in mental status in less than 48 h or improvement of more than two grades in mental

status.
  ○ Complete response was defined as recovery to normal mental status with no evidence of asterixis.
  ○ Partial response was defined as improvement in mental status by at least two grades without normalization.
 • Therapeutic failure was defined as:
  ○ no change in mental state after 48 h of therapy;
  ○ sustained deterioration of 1 grade in mental state during 48 h of therapy;
  ○ deterioration of 2 grades in mental state; and
  ○ death in coma despite treatment.
 • Participants who failed treatment on sodium benzoate were unblinded, and received lactulose; participants who failed treated with lactulose continued with the same treatment.
 • The trial authors were contacted for more information regarding random sequence generation, serious and non-serious adverse events; quality-of-life measures and liver-related mortality. No response was received.
Funding:
 • No information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	An independent healthcare worker administered the treatments. However, it may be obvious to a participant if they are receiving lactulose, due to dose titration and the laxative effect
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	The assessment of response was conducted by a blinded trial author
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants who did not complete some of the tests were not included in the analyses. However, it is unclear whether all participants were included in the assessment of the primary outcomes
Selective reporting (reporting bias)	Low risk	The trial reported clinically relevant outcomes in full. The original trial protocol was not available
Other bias	Low risk	None identified

Overall assessment Non-mortality outcomes	High risk	
Overall assessment Mortality outcomes	High risk	

Uribe 1990

Methods	**Sodium benzoate:** multicentre, double-blind, randomised clinical trial
Participants	**Included participants:** cirrhosis with chronic Grade 1 or 2 hepatic encephalopathy (n = 27) **Age** (mean ± SD): • sodium benzoate group 58 ± 8 years • lactitol group 58 ± 11 years **Proportion of men:** • sodium benzoate group 41.7% • lactitol group 53.3% **Aetiology of liver disease:** • alcohol: 55.6% • 'postnecrotic': 40.7% • cryptogenic: 3.7% **MELD score:** not reported
Interventions	**Intervention comparison:** sodium benzoate vs lactitol both given orally as a syrup **Sodium benzoate:** mean 5.6 g/day (n = 12) **Lactitol:** mean 29.1 g/day (n = 15) **Duration of treatment:** 2 weeks **Co-intervention:** all participants received lactitol, titrated to produce 2-3 soft stools/day, for 1 week prior to randomisation
Outcomes	**Neurocognitive assessment:** PSE Sum and Index comprising: • mental status (West Haven Criteria) • asterixis • Number Connection Test A • blood ammonia • electroencephalography
Inclusion period	Not reported
Country of origin	Mexico
Outcomes included in meta-analyses	• Mortality • Hepatic encephalopathy • Serious adverse events • Non-serious adverse events • Blood ammonia

Notes	**Publication status:** • the trial was published as a full paper in Spanish but an English translation was available. We contacted the trial authors who provided additional data and information regarding randomisation and funding **Funding:** • Supported by Fundacion Clinica Medica Sur and Fundacion Mexicana Para La Salud

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, and personnel measuring participants' mental state, were blinded to their allocation group
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Personnel measuring participants' mental state were blinded to their allocation group
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data and all participants were included in the analyses
Selective reporting (reporting bias)	Low risk	No reporting bias identified
Other bias	Low risk	None identified
Overall assessment Non-mortality outcomes	Low risk	
Overall assessment Mortality outcomes	Low risk	

Rockey 2014

Methods	**Glycerol phenylbutyrate:** multicentre, double-blind, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis with 2 episodes of hepatic encephalopathy at West Haven Grade 2 or higher in the previous 6 months, 1 of which was within 3 months of randomisation (n = 178); 91% in the glycerol phenylbutyrate group and 92% in the placebo group had no evidence of hepatic encephalopathy at trial entry but the majority

	were on treatment with lactulose or rifaximin or both **Age** (mean ± SD): • glycerol phenylbutyrate group 53.8 ± 8.9 years • placebo group 55.4 ± 8.8 years **Proportion of men:** • glycerol phenylbutyrate group 50% • placebo group 67% **Aetiology of liver disease:** not reported **MELD score** (mean ± SD): • glycerol phenylbutyrate group 12.6 ± 3.7 • placebo group 12.3 ± 3.8
Interventions	**Intervention comparison:** oral glycerol phenylbutyrate vs placebo **Glycerol phenylbutyrate:** 6 mL twice daily (n = 90) **Placebo:** identically presented but not specified (n = 88) **Duration of treatment:** 16 weeks **Co-intervention:** *Lactulose* use at baseline (mL/day) • glycerol phenylbutyrate n = 72; median 45 (5-266) mL/day • placebo n = 65; median 45 (15-160) mL/day *Rifaximin* use at baseline (mg/day); participants in the USA were eligible if they had experienced at least 1 of their 2 qualifying episodes of hepatic encephalopathy after ≥ 1 month rifaximin treatment • glycerol phenylbutyrate n = 30; median 1100 (550-1200) mg/day • placebo n = 29; median 1100 (400-1650) mg/day
Outcomes	**Neuropsychiatric assessment:** • mental status (West Haven Criteria) • asterixis grade • venous blood ammonia **Others:** • time to first episode of hepatic encephalopathy • total number of episodes of hepatic encephalopathy
Inclusion period	1 June 2010-31 October 2011
Country of origin	51 centres, including 35 in the USA, 7 in the Ukraine, and 9 in Russia
Outcomes included in meta-analyses	• Mortality • Hepatic encephalopathy • Serious adverse events • Non-serious adverse events • Venous blood ammonia
Notes	**Publication status:** full paper • Primary endpoint: the proportion of participants experiencing an episode of hepatic encephalopathy, defined as either the development of West Haven Grade ≥ 2 change or an increase ≥ 1 in both the West Haven and asterixis grade, if West Haven Grade 0 at baseline

	• Secondary endpoints: included time to the first episode of hepatic encephalopathy; total episodes of hepatic encephalopathy
	• Assessment by caregiver based on the CHESS used as a safety check
	• More participants randomised to glycerol phenylbutyrate than placebo where Childs Class C (21 versus 8, respectively)
	• Precipitating factors were most commonly listed as unknown or other, followed by dehydration, infection, constipation, excess dietary protein, and use of sedatives
	• The treatment effect of glycerol phenylbutyrate was more pronounced in the 119 participants who were not taking rifaximin at entry compared to the 59 who were. However, there was no difference in primary or secondary outcomes between treatment arms in the 59 participants who were taking rifaximin at entry.
	• The authors of the trial were contacted for more information regarding the aetiology of participants' cirrhosis; and data relating to quality-of-life and the Number Connection Test results. No reply was received.
	Funding:
	• Trial sponsored by Hyperion Therapeutics, Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All trial personnel, participants and caregivers were blinded to treatment group assignment
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	The primary efficacy measure was adjudicated by the blinded investigators during the study and analysed after unblinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcome data. However, more participants randomised to glycerol phenylbutyrate exited the study before completion than participants receiving placebo
Selective reporting (reporting bias)	Low risk	All clinically relevant outcomes were reported.
Other bias	Low risk	None
Overall assessment Non-mortality outcomes	High risk	

Rockey 2014 *(Continued)*

Overall assessment Mortality outcomes	High risk	

STOP-HE 2017

Methods	**Ornithine phenylacetate (OCR-002):** multicentre, double-blind, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis, with an acute episode of overt hepatic encephalopathy ≥ Grade 2 and hyperammonaemia, whose mental status did not improve after a minimum of 12 h of 'standard care' (n = 231) **Age:** not reported **Proportion of men:** USA 59%; elsewhere 72% **Aetiology of liver disease:** not reported **MELD score** (mean): USA 20; elsewhere 18
Interventions	**Intervention comparison:** ornithine phenylacetate vs placebo **Ornithine phenylacetate:** 10 g/day, 15 g/day or 20 g/day, by continuous IV infusion (n = 116); dose pre-determined by the level of hepatic decompensation **Placebo:** identically presented 5% dextrose by continuous IV infusion (n = 115) **Duration of treatment:** 5 days **Co-intervention:** all participants received 'standard care'" based on 'gut flora modification'" but this was not specified although 135 (58.4%) participants were taking rifaximin (mean dose: 1057 mg/day; range: 400-1650/day); 12 (5.2%) were taking L-ornithine L-aspartate (dose range 9-20g/day) and an unspecified proportion were taking lactulose

Outcomes	**Neurocognitive assessment:**
	• clinical improvement in hepatic encephalopathy symptoms assessed with HESA; no details provided
	  • venous blood ammonia
	  • median time to improvement
	  • time to normal plasma ammonia levels
	  • reduction in plasma ammonia levels
	  • correlation of ammonia levels with clinical improvement

Inclusion period	November 2013-December 2016
Country of origin	Australia, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Israel, Italy, Netherlands, New Zealand, Russian Federation, Spain, USA
Outcomes included in meta-analyses	• Mortality • Serious adverse events • Non-serious adverse events • Venous blood ammonia
Notes	**Publication status:** 3 separate abstracts at the same conference • No extractable data are available in the abstracts for the primary end-points. • Differences, some of them significant, were observed between participants

	enrolled in the USA (n = 130) and elsewhere (n = 101) in baseline characteristics, the severity of the underlying liver disease, the precipitant factors and use of additional anti-encephalopathy treatments **Funding:** • Trial sponsored by Ocera Therapeutics Inc	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, care providers, investigators and outcomes assessors were blinded
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Participants, care providers, investigators and outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. All participants were included in the analyses
Selective reporting (reporting bias)	High risk	The primary end-point in the registered trial protocol is '*change from baseline in hepatic encephalopathy stage*'. However, in the published abstracts the primary end-point reported is '*the time to meaningful clinical improvement in hepatic encephalopathy symptoms assessed using the Hepatic Encephalopathy Staging Tool*' together with a number of other time-related variables.
Other bias	High risk	Differences were reported for a number of variables in participants recruited in the USA and those recruited elsewhere in the world, which is an additional source of bias
Overall assessment Non-mortality outcomes	High risk	
Overall assessment Mortality outcomes	High risk	

Ventura-Cots 2016

Methods	**Ornithine phenylacetate (OCR-002):** two-centre, double-blind, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis, enrolled within 24 h of an upper gastrointestinal bleed (n = 38). Three people in each group had hepatic encephalopathy at the time of randomisation **Age** (mean ± SD): • ornithine phenylacetate group 55 ± 10 years • placebo group 56 ± 11 years **Proportion of men:** • ornithine phenylacetate group 70% • placebo group 66% **Aetiology of liver disease** (ornithine phenylacetate: placebo group): • alcohol 70%: 44.4% • hepatitis C virus 5%: 33.3% • hepatitis C virus and alcohol 10%: 5.6% • others 15%: 16.7% **MELD score** (mean ± SD): • ornithine phenylacetate group 11.6 ± 4.4 • placebo group 12.2 ± 3.9
Interventions	**Intervention comparison:** ornithine phenylacetate vs placebo **Ornithine phenylacetate:** 10 g/day by continuous IV infusion at a rate of 0.416 g/h (n = 20) **Placebo:** identically presented glucose-saline solution by continuous IV infusion (n = 18) **Duration of treatment:** 5 days **Co-intervention:** all participants received standard care which included: • IV ceftriaxone 1 g/day • lactulose initially given as an enema 12 hourly; then orally, adjusted to produce 2 - 3 bowel movements/day
Outcomes	**Neurocognitive assessment:** • hepatic encephalopathy, measured using the West Haven Criteria, and CHESS • venous blood ammonia at 24 h (primary measure), and at any time-point (secondary outcome) **Others:** • pharmacokinetic profiles of the drug and its metabolites • safety and tolerability of the drug • bacterial infections during treatment
Inclusion period	September 2012 - August 2014
Country of origin	Spain
Outcomes included in meta-analyses	• Mortality • Hepatic encephalopathy • Serious adverse events • Non-serious adverse events

Ventura-Cots 2016   (*Continued*)

Notes	**Publication status:** full paper
	• This trial was designed primarily to assess the efficacy of ornithine phenylacetate as an ammonia-lowering agent versus placebo in people with cirrhosis after an upper gastrointestinal bleed. The primary outcome was the decrease in venous plasma ammonia at 24 h.
	• The trial authors were contacted for more information regarding changes in participants' blood ammonia concentrations during the time course of the study but these data were not retrievable.
	Funding:
	• Trial sponsored by Ocera Therapeutics Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Correspondence with the trial authors confirmed the use of sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded. The pharmacy department prepared the infusion solutions independently
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Data were independently monitored by a separate institution. A data-blind review was conducted before locking the trial database
Incomplete outcome data (attrition bias) All outcomes	Low risk	Correspondence with the trial authors confirmed use of ITT analyses
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported.
Other bias	Low risk	None identified
Overall assessment Non-mortality outcomes	Low risk	
Overall assessment Mortality outcomes	Low risk	

Bajaj 2013

Methods	**AST-120 (spherical carbon absorbant):** multicentre, double-blind, placebo-controlled, dose-ranging, randomised clinical trial
Participants	**Included participants:** compensated cirrhosis (MELD score < 25) and covert hepatic encephalopathy (minimal and Grade 1) (n = 148) **Age** (mean): 55 years **Proportion of men:** not reported **Aetiology of liver disease:** • alcohol: not reported • hepatitis C virus: 53% **MELD score** (mean): 10
Interventions	**Intervention comparison:** oral AST-120 vs placebo **AST-120:** 6 g/day (n = 50), 12 g/day (n = 50) **Placebo:** no details provided (n = 48) **Duration of treatment:** 8 weeks **Co-intervention:** none reported
Outcomes	**Neurocognitive assessment:** • West Haven Criteria • RBANS • PHES battery • clinical global assessment of hepatic encephalopathy • venous blood ammonia
Inclusion period	March 2009-June 2010
Country of origin	USA
Outcomes included in meta-analyses	• Mortality • Venous blood ammonia
Notes	**Publication status:** abstract; unpublished information about trial methods (randomisation) received from the trial authors • The primary endpoint was neurocognitive improvement, defined as a change in global RBANS at 8-weeks compared to baseline. • The trial report does not describe the number of participants with an overall improvement in neurocognitive status. We were therefore unable to include the trial in our meta-analysis of this outcome. • The trial report does not describe whether adverse events were classified as serious or non-serious. We were therefore unable to include the trial in our meta-analysis of this outcome. • The authors have stated that the results were confounded by the study design, which allowed for an improvement in neurocognitive measures before drug randomisation. • We included data from the group receiving the highest dose of AST-120 in the analysis of blood ammonia changes. **Funding:** • Trial sponsored by Ocera Therapeutic Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel using placebo
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Blinding of outcome assessment using placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and included in the analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes were reported. Outcomes in the published abstract correspond with the published protocol
Other bias	Low risk	None identified
Overall assessment Non-mortality outcomes	Low risk	
Overall assessment Mortality outcomes	Low risk	

Pockros 2009

Methods	**AST-120 (spherical carbon absorbant):** multicentre, open-label, clinical trial
Participants	**Included participants:** cirrhosis (MELD score ≤ 15) and hepatic encephalopathy Grades 1 or 2 using West Haven Criteria (n = 47) **Age:** not reported **Proportion of men:** not reported **Aetiology of liver disease:** not reported **MELD score:** not reported
Interventions	**Intervention comparison:** oral AST-120 vs lactulose **AST-120:** 2 g 4 times/day (n = 24) **Lactulose:** no details reported (n = 23) **Duration of treatment:** 4 weeks **Co-intervention:** some participants were taking lactulose on admission: this was stopped

	in the participants randomised to AST-120
Outcomes	**Neurocognitive assessment:** • mental status (West Haven Criteria) • HESA • venous blood ammonia
Inclusion period	September 2007 - June 2009
Country of origin	USA
Outcomes included in meta-analyses	• Mortality • Hepatic encephalopathy • Venous blood ammonia
Notes	**Publication status:** abstract • Participants were classified using West Haven Criteria as Grade 1 or 2 hepatic encephalopathy but, based on the HESA score, were predominantly Grade 0. • The trial report describes non-serious adverse events including diarrhoea and flatulence, but does not provide the number or proportion of participants affected. • The trial authors provided further information regarding random sequence generation. **Funding:** • Trial sponsored by Ocera Therapeutic Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial without blinding
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open-label trial without blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Evaluable data are available for 41 participants: 3 participants randomised to lactulose were excluded because of non-compliance; 3 participants randomised to AST-120 were excluded for 'other reasons'

Selective reporting (reporting bias)	Low risk	The outcomes reported in the published abstract correspond to the outcomes listed in the trial protocol
Other bias	Low risk	None identified
Overall assessment Non-mortality outcomes	High risk	
Overall assessment Mortality outcomes	High risk	

Naderian 2017

Methods	**PEG:** single-centre, double-blind, randomised clinical trial
Participants	**Included participants:** cirrhosis with an acute episode of overt hepatic encephalopathy (n = 40) **Age** (mean ± SD): • PEG group 53.6 ± 11.6 years • lactulose group 59.6 ± 9.2 years **Proportion of men:** • PEG group 76% • lactulose group 58% **Aetiology of liver disease** (PEG: lactulose group): • alcohol 4.8%: 5.3% • cryptogenic 23.8%: 31.6% • hepatitis B 28.6%: 31.6% • hepatitis C 23.8%: 21.1% • non-alcoholic steatohepatitis 4.8%: 5.3% • portal thrombosis 9.5%: 0% • primary sclerosing cholangitis 4.8%: 0% **MELD score** (median ± interquartile range): • PEG group 17.5 ± 15 • lactulose group 17.5 ± 6
Interventions	**Intervention comparison:** PEG plus lactulose vs lactulose **PEG:** 280 g PEG in 4 L water as a single dose over 30-120 min. In addition lactulose was administered in the same amount enterally or rectally as in the control group (n = 21) **Lactulose:** 20-30 g lactulose administered orally or via nasogastric tube (at least 3 doses in 24 h) or 200 g administered via rectal tube (n = 19) **Duration of treatment:** 24 h **Co-intervention:** none reported
Outcomes	**Neurocognitive assessment:** • HESA • blood ammonia

	Others • length of hospitalisation
Inclusion period	September 2015 - January 2016
Country of origin	Iran
Outcomes included in meta-analyses	• Mortality • Hepatic encephalopathy • Adverse events • Blood ammonia
Notes	**Publication status:** full paper • The primary end-point was improvement in at least 1 grade on the HESA at 24 h • The trial authors were contacted for more details regarding blinding of participants and personnel - the required information was provided. **Funding:** • No funding from industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, block randomisation (block size 6 participants)
Allocation concealment (selection bias)	Low risk	One team member was responsible for prescribing the trial drugs, while assessments of HESA scores at presentation and at 24 h were done by another team member blinded to the allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded. The statistical analysis was undertaken by a blinded analyst
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Outcome assessors were independent from the people who prescribed the study drugs
Incomplete outcome data (attrition bias) All outcomes	High risk	Four of the original 48 eligible participants refused consent, while a further 4 (1 allocated to PEG; 3 allocated to lactulose) were excluded from the analyses because they had received sedative drugs
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes are reported.
Other bias	Low risk	None identified

Overall assessment Non-mortality outcomes	High risk	
Overall assessment Mortality outcomes	High risk	

Rahimi 2014

Methods	**PEG:** single-centre, open-label, randomised clinical trial. The HELP study
Participants	**Included participants:** cirrhosis and any grade of overt hepatic encephalopathy (n = 50) **Age** (mean ± SD): • PEG group 56 ± 7 years • lactulose group 56 ± 11 years **Proportion of men:** • PEG group 64% • lactulose group 60% **Aetiology of liver disease** (PEG, lactulose group): • alcohol 40%, 36% • cryptogenic 24%, 24% • hepatitis C 32%, 36% • hepatitis B 4%, 4% **MELD score** (mean ± SD): • PEG group 17 ± 6 • lactulose group 17 ± 5
Interventions	**Intervention comparison:** PEG vs lactulose **PEG:** 3350-electrolyte solution; 4 L given as a single dose over 4 h (n = 25) **Lactulose:** 20-30 g lactulose administered orally or via nasogastric tube (at least 3 doses in 24 h) or 200 g administered via rectal tube (n = 25) **Duration of treatment:** 24 h **Co-intervention:** participants were allowed to receive a single dose of lactulose prior to randomisation, and after 24 h of treatment regardless of their group allocation
Outcomes	**Neuropsychiatric assessment:** • HESA • blood ammonia at baseline and 24 h **Others:** • time to resolution of hepatic encephalopathy • overall length of hospitalisation
Inclusion period	January 2011-June 2012
Country of origin	USA
Outcomes included in meta-analyses	• Mortality • Hepatic encephalopathy • Serious adverse events

| | • Non-serious events |
| | • Blood ammonia |

Notes	**Publication status:** full paper
	• Baseline blood urea nitrogen concentrations were significantly higher in the participants randomised to the PEG group.
	• One participant in the PEG group received a lactulose enema due to inability to site the nasogastric tube. One additional participant in the PEG group was discharged before the study was complete, and one refused to continue.
	• The primary end point was an improvement of 1 or more HESA grade at 24 h,
	Funding:
	• No conflicts of interest identified. Funding was received from national grants; these had no influencing role in the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated number and treatment assignment
Allocation concealment (selection bias)	Low risk	Participants' allocation was concealed in opaque sealed envelopes. In some participants one investigator obtained consent, randomised the participants and ensured that the appropriate study medication was administered while the follow-up was undertaken by another investigator
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	A separate, blinded investigator conducted the assessment of neuropsychological status after randomisation
Incomplete outcome data (attrition bias) All outcomes	High risk	All analyses were conducted as ITT. Two participants did not achieve the full 24-h follow-up and so data are missing for the assessment of neuropsychological status. One participant in the PEG group did not receive the allocated treatment and so was treated with a lactulose enema. Two participants in the PEG group did not have follow-up HESA scores; of these one became alert and oriented and refused assessment while the other improved to point of discharge home in less than 24 h. Conse-

		quently, these two participants were not included in either the initial or 24-h analysis
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported. However, non-serious adverse events were not extractable
Other bias	High risk	The blood urea nitrogen level was significantly higher in the participants randomised to PEG
Overall assessment Non-mortality outcomes	High risk	
Overall assessment Mortality outcomes	High risk	

Shehata 2018

Methods	**PEG:** single-centre, open label, randomised clinical trial
Participants	**Included participants:** people admitted with cirrhosis and an acute episode of overt hepatic encephalopathy (n = 100) **Age** (mean ± SD)**:** • PEG group 56.4 ± 8.6 years • lactulose group 54.5 ± 11.8 years **Proportion of men:** • PEG group 44% • lactulose group 60% **Aetiology of liver disease**: all participants had hepatitis C-related cirrhosis
Interventions	**PEG:** single dose (3 sachets if participant < 75 kg or 4 sachets if participant > 75 kg) administered orally over 3-4 h or via a nasogastric tube at a rate of 20-30 mL/min. Each sachet contained 64 g PEG dissolved in 1 L tap water **Lactulose:** 20-30 mL lactulose orally or via nasogastric tube, given as 3 doses over 24 h. 200 mL lactulose and plain water also given as a retention enema every 4 h
Outcomes	**Primary:** at least 1 scale improvement in the HESA score after 24 h **Secondary:** length of hospital stay, adverse events
Inclusion period	May-December 2017
Country of origin	Egypt
Outcomes included in meta-analyses	• Mortality • Hepatic encephalopathy • Adverse events

Notes	**Publication status:** full paper • The registered trial number cited in the published paper is incorrect; the corrected number, later provided by the trial authors, is NCT03100513. The study was completed 18 months earlier than anticipated, although it is still registered as 'recruiting'. **Funding:** • No funding from industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation (block size 10 participants)
Allocation concealment (selection bias)	Low risk	Participant allocation was in opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators were blinded to the random code sequence. Participants and personnel administering the treatments were not blinded
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Participants were identified only by code numbers
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses. Those lost to follow-up were evaluated using ITT analyses except for adverse events
Selective reporting (reporting bias)	Low risk	All clinically relevant predefined outcomes were reported. Changes in blood ammonia levels were not reported
Other bias	Low risk	None identified
Overall assessment Non-mortality outcomes	High risk	
Overall assessment Mortality outcomes	High risk	

CHESS: Clinical Hepatic Encephalopathy Staging Scale; **HESA:** Hepatic Encephalopathy Scoring Algorithm; **ITT:** intention-to-treat; **IV:** intravenous; **MELD:** Model for End-stage Liver Disease; **PEG:** polyethylene glycol; **PHES:** Psychometric Hepatic Encephalopa-

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thy Score; **PSE:** Portal-Systemic Encephalopathy; **RBANS:** Repeatable Battery for the Assessment of Neuropsychological Status; **SD:** standard deviation

Characteristics of excluded studies *[author-defined order]*

Study	Reason for exclusion
Campollo 1992	**Sodium benzoate:** 18 participants with cirrhosis and chronic persistent hepatic encephalopathy were treated for 6 months with oral sodium benzoate in a mean dose of 6.4 g/day given as an 8% solution We excluded this study as it was observational.
Mendenhall 1986	**Sodium benzoate:** double-blind, cross-over, randomised clinical trial, undertaken in 8 participants with overt hepatic encephalopathy allocated to oral sodium benzoate or sodium phenylacetate We excluded this trial because it compared sodium benzoate with another ammonia-lowering agent
Panella 1993	**Sodium benzoate:** double-blind, cross-over, randomised clinical trial undertaken in 7 participants with cirrhosis and stable Grade 1-2 hepatic encephalopathy randomised to sodium benzoate or placebo as an adjuvant to treatment with branched chain amino acids; participants were crossed over to the alternative arm after 7 days. Lactulose and the antibiotic Colimicin were added to standard treatment but it is unclear whether this was provided equally in both groups. Participants receiving adjuvant sodium benzoate showed a significant reduction in blood ammonia levels compared to the group receiving placebo and a trend to a greater reduction in Number Connection Test times and the PSE Index We excluded this trial as it was not a direct comparison of the drug of interest against either placebo or another active agent
Ghabril 2013	**Glycerol phenylbutyrate:** open-label, phase IIa study designed to evaluate the safety, tolerability and effect on blood ammonia concentrations of 2 doses of glycerol phenylbutyrate in 15 participants with cirrhosis and a history of at at least 2 previous episodes of overt hepatic encephalopathy We excluded this trial as it was observational.
Weiss 2018	**Sodium phenylbutyrate:** 18 participants with cirrhosis, overt hepatic encephalopathy and hyperammonaemia admitted to an ICU were given sodium phenylbutyrate 200 mg/kg/day orally or via a nasogastric tube until blood ammonia levels returned to normal on 2 consecutive occasions or until neurological status improved. Other treatments such as lactulose or rifaximin, were maintained if prescribed before inclusion. The results in this group were compared with those in an historical control group (matched for age, sex, MELD score, and severity of hepatic encephalopathy using West Haven Criteria), managed in the same unit, using the same guidelines We excluded this trial as it was observational.

ICU: intensive care unit; **MELD:** Model for End-stage Liver Disease; **PSE:** Portal-Systemic Encephalopathy (see Table 2)

Characteristics of ongoing studies *[ordered by study ID]*

NCT00558038

Trial name or title	**AST-120** Randomized trial comparing the efficacy of AST-120 versus lactulose for treatment of mild hepatic encephalopathy
Methods	Open-label, randomised clinical trial
Participants	End-stage liver disease with a MELD score < 16 and Grade 1-2 hepatic encephalopathy (n = 40)
Interventions	**AST-120:** 2 g sachets 4 times/day **Lactulose:** as previously prescribed or started at 30 mL twice and titrated to produce 2-3 soft stools/day
Outcomes	**Primary:** change in West Haven grade over 4 weeks **Secondary:** change in the HESA, ammonia levels, serum bile acid and amino acid profiles, itching (visual analogue scale), asterixis, clinical laboratory tests, clinical examination
Starting date	September 2007
Contact information	Paul Pockros, Scripps Clinic
Country of origin	USA
Notes	Phase 2 study; completed on 30 May 2014

NCT03448770

Trial name or title	**PEG:** To compare efficacy and safety of lactulose versus polyethylene glycol for treatment of overt hepatic encephalopathy in cirrhotics; a randomised controlled trial
Methods	Open-label, randomised clinical trial
Participants	Cirrhosis and hepatic encephalopathy of Grade 2 and above (n = 110)
Interventions	**PEG:** 17 g administered orally or via nasogastric tube 3-4 times/day **Lactulose:** 20-30 g lactulose administered orally or via nasogastric tube (at least 3 doses in 24 h) or 200 g administered via rectal tube
Outcomes	**Primary:** complete reversal of hepatic encephalopathy (Grade 0) **Secondary:** improvement in hepatic encephalopathy by 2 grades; length of ICU stay; presence of EED changes; adverse events
Starting date	1 August 2017
Contact information	Dr Abhinav Verma, abhinav.3183@gmail.com

Country of origin	India
Notes	The estimated final data collection date for the primary outcome measure and for study completion was 31 July 2018

EEG: electroencephalogram;**HESA:** Hepatic Encephalopathy Scoring Algorithm; **ICU:** intensive care unit; **MELD:** Model for End-stage Liver Disease; **PEG:** Polyethylene glycol;

D A T A   A N D   A N A L Y S E S

Comparison 1.   Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	11		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Sodium benzoate versus placebo	1	16	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Sodium benzoate versus lactulose/lactitol	2	101	Risk Ratio (IV, Random, 95% CI)	1.26 [0.49, 3.28]
1.3 Glycerol phenylbutyrate versus placebo	1	178	Risk Ratio (IV, Random, 95% CI)	0.65 [0.11, 3.81]
1.4 Ornithine phenylacetate versus placebo	2	269	Risk Ratio (IV, Random, 95% CI)	0.73 [0.35, 1.51]
1.5 AST-120 versus placebo	1	148	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 AST-120 versus lactulose	1	41	Risk Ratio (IV, Random, 95% CI)	1.05 [0.59, 1.85]
1.7 Polyethylene glycol versus lactulose	3	190	Risk Ratio (IV, Random, 95% CI)	0.5 [0.09, 2.64]
2 Hepatic encephalopathy	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1 Sodium benzoate versus lactulose/lactitol	1	74	Risk Ratio (IV, Random, 95% CI)	1.22 [0.51, 2.93]
2.2 Glycerol phenylbutyrate versus placebo	1	178	Risk Ratio (IV, Random, 95% CI)	0.57 [0.36, 0.90]
2.3 Ornithine phenylacetate versus placebo	1	38	Risk Ratio (IV, Random, 95% CI)	2.71 [0.12, 62.70]
2.4 AST-120 versus lactulose	1	41	Risk Ratio (IV, Random, 95% CI)	1.05 [0.59, 1.85]
2.5 Polyethylene glycol versus lactulose	3	190	Risk Ratio (IV, Random, 95% CI)	0.19 [0.08, 0.44]
3 Serious adverse events	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Sodium benzoate versus placebo	1	16	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Sodium benzoate versus lactulose/lactitol	2	101	Risk Ratio (IV, Random, 95% CI)	1.08 [0.44, 2.68]
3.3 Glycerol phenylbutyrate versus placebo	1	178	Risk Ratio (IV, Random, 95% CI)	1.63 [0.85, 3.13]
3.4 Ornithine phenylacetate versus placebo	2	264	Risk Ratio (IV, Random, 95% CI)	0.92 [0.62, 1.36]
3.5 AST-120 versus lactulose	1	41	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Polyethylene glycol versus lactulose	3	190	Risk Ratio (IV, Random, 95% CI)	0.57 [0.18, 1.82]
4 Non-serious adverse events	8		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Sodium benzoate versus placebo	1	16	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Sodium benzoate versus lactulose/lactitol	2	182	Risk Ratio (IV, Random, 95% CI)	1.13 [0.96, 1.32]
4.3 Glycerol phenylbutyrate versus placebo	1	178	Risk Ratio (IV, Random, 95% CI)	1.04 [0.88, 1.21]

4.4 Ornithine phenylacetate versus placebo	2	269	Risk Ratio (IV, Random, 95% CI)	1.08 [0.78, 1.51]
4.5 Polyethylene glycol versus lactulose	2	137	Risk Ratio (IV, Random, 95% CI)	0.71 [0.43, 1.18]
5 Ammonia	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Sodium benzoate versus placebo	1	16	Mean Difference (IV, Random, 95% CI)	-32.0 [-46.85, -17.15]
5.2 Sodium benzoate versus lactulose/lactitol	2	85	Mean Difference (IV, Random, 95% CI)	9.00 [-1.10, 19.11]
5.3 Glycerol phenylbutyrate versus placebo	1	178	Mean Difference (IV, Random, 95% CI)	-12.0 [-23.37, -0.63]
5.4 Ornithine phenylacetate versus placebo	1	231	Mean Difference (IV, Random, 95% CI)	-27.10 [-48.55, -5.65]
5.5 AST-120 versus placebo	1	98	Mean Difference (IV, Random, 95% CI)	-22.0 [-26.75, -17.25]
5.6 AST-120 versus lactulose	1	35	Mean Difference (IV, Random, 95% CI)	5.2 [-2.75, 13.15]
5.7 Polyethylene glycol versus lactulose	2	90	Mean Difference (IV, Random, 95% CI)	-29.28 [-95.96, 37.39]

Analysis 1.1.   Comparison 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol, Outcome 1 Mortality.

Review: Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis

Comparison: 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Sodium benzoate versus placebo					
Gonzalez 1994	0/7	0/9			Not estimable
Subtotal (95% CI)	**7**	**9**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Sodium benzoate versus lactulose/lactitol					
Sushma 1992	8/38	6/36	■	100.0 %	1.26 [0.49, 3.28]
Uribe 1990	0/12	0/15			Not estimable
Subtotal (95% CI)	**50**	**51**	◆	**100.0 %**	**1.26 [0.49, 3.28]**
Total events: 8 (Treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					

0.005   0.1   1   10   200

Treatment   Control

(*Continued* . . .)

Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV,Random,95% CI		IV,Random,95% CI
3 Glycerol phenylbutyrate versus placebo					
Rockey 2014	2/90	3/88		100.0 %	0.65 [0.11, 3.81]
Subtotal (95% CI)	**90**	**88**		**100.0 %**	**0.65 [0.11, 3.81]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
4 Ornithine phenylacetate versus placebo					
STOP-HE 2017	11/116	15/115		100.0 %	0.73 [0.35, 1.51]
Ventura-Cots 2016	0/20	0/18			Not estimable
Subtotal (95% CI)	**136**	**133**		**100.0 %**	**0.73 [0.35, 1.51]**
Total events: 11 (Treatment), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
5 AST-120 versus placebo					
Bajaj 2013	0/100	0/48			Not estimable
Subtotal (95% CI)	**100**	**48**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 AST-120 versus lactulose					
Pockros 2009	11/20	11/21		100.0 %	1.05 [0.59, 1.85]
Subtotal (95% CI)	**20**	**21**		**100.0 %**	**1.05 [0.59, 1.85]**
Total events: 11 (Treatment), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					
7 Polyethylene glycol versus lactulose					
Naderian 2017	0/21	0/19			Not estimable
Rahimi 2014	1/25	2/25		50.7 %	0.50 [0.05, 5.17]
Shehata 2018	1/50	2/50		49.3 %	0.50 [0.05, 5.34]
Subtotal (95% CI)	**96**	**94**		**100.0 %**	**0.50 [0.09, 2.64]**
Total events: 2 (Treatment), 4 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 1 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 0.82 (P = 0.41)					

```
        0.005    0.1    1    10    200
            Treatment      Control
```

Analysis 1.2.   Comparison 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol, Outcome 2 Hepatic encephalopathy.

Review: Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis

Comparison: 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol

Outcome: 2 Hepatic encephalopathy

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Sodium benzoate versus lactulose/lactitol					
Sushma 1992	9/38	7/36		100.0 %	1.22 [0.51, 2.93]
Subtotal (95% CI)	**38**	**36**		**100.0 %**	**1.22 [0.51, 2.93]**
Total events: 9 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
2 Glycerol phenylbutyrate versus placebo					
Rockey 2014	21/90	36/88		100.0 %	0.57 [0.36, 0.90]
Subtotal (95% CI)	**90**	**88**		**100.0 %**	**0.57 [0.36, 0.90]**
Total events: 21 (Treatment), 36 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.44 (P = 0.015)					
3 Ornithine phenylacetate versus placebo					
Ventura-Cots 2016	1/20	0/18		100.0 %	2.71 [0.12, 62.70]
Subtotal (95% CI)	**20**	**18**		**100.0 %**	**2.71 [0.12, 62.70]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.62 (P = 0.53)					
4 AST-120 versus lactulose					
Pockros 2009	11/20	11/21		100.0 %	1.05 [0.59, 1.85]
Subtotal (95% CI)	**20**	**21**		**100.0 %**	**1.05 [0.59, 1.85]**
Total events: 11 (Treatment), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					
5 Polyethylene glycol versus lactulose					
Naderian 2017	1/21	5/19		16.1 %	0.18 [0.02, 1.41]
Rahimi 2014	2/25	12/25		35.2 %	0.17 [0.04, 0.67]
Shehata 2018	3/50	14/50		48.6 %	0.21 [0.07, 0.70]
Subtotal (95% CI)	**96**	**94**		**100.0 %**	**0.19 [0.08, 0.44]**
Total events: 6 (Treatment), 31 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.08, df = 2 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 3.93 (P = 0.000084)					

```
        0.01   0.1    1    10   100
            Treatment    Control
```

Analysis 1.3. Comparison 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol, Outcome 3 Serious adverse events.

Review: Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis

Comparison: 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol

Outcome: 3 Serious adverse events

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Sodium benzoate versus placebo					
Gonzalez 1994	0/7	0/9			Not estimable
Subtotal (95% CI)	**7**	**9**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Sodium benzoate versus lactulose/lactitol					
Sushma 1992	8/38	7/36		100.0 %	1.08 [0.44, 2.68]
Uribe 1990	0/12	0/15			Not estimable
Subtotal (95% CI)	**50**	**51**		**100.0 %**	**1.08 [0.44, 2.68]**
Total events: 8 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.86)					
3 Glycerol phenylbutyrate versus placebo					
Rockey 2014	20/90	12/88		100.0 %	1.63 [0.85, 3.13]
Subtotal (95% CI)	**90**	**88**		**100.0 %**	**1.63 [0.85, 3.13]**
Total events: 20 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					
4 Ornithine phenylacetate versus placebo					
STOP-HE 2017	29/114	33/112		86.9 %	0.86 [0.56, 1.32]
Ventura-Cots 2016	6/20	4/18		13.1 %	1.35 [0.45, 4.03]
Subtotal (95% CI)	**134**	**130**		**100.0 %**	**0.92 [0.62, 1.36]**
Total events: 35 (Treatment), 37 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.56, df = 1 (P = 0.46); I² =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
5 AST-120 versus lactulose					
Pockros 2009	0/20	0/21			Not estimable
Subtotal (95% CI)	**20**	**21**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					

0.005   0.1   1   10   200

Treatment   Control

(*Continued* . . .)

Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV,Random,95% CI		IV,Random,95% CI

Test for overall effect: not applicable

6 Polyethylene glycol versus lactulose

Naderian 2017	0/21	0/19			Not estimable
Rahimi 2014	3/25	5/25		76.3 %	0.60 [0.16, 2.25]
Shehata 2018	1/50	2/50		23.7 %	0.50 [0.05, 5.34]
Subtotal (95% CI)	**96**	**94**		**100.0 %**	**0.57 [0.18, 1.82]**

Total events: 4 (Treatment), 7 (Control)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.02, df = 1 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 0.94 (P = 0.35)

0.005 0.1 1 10 200

Treatment   Control

Analysis 1.4. Comparison 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol, Outcome 4 Non-serious adverse events.

Review: Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis

Comparison: 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol

Outcome: 4 Non-serious adverse events

Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV,Random,95% CI		IV,Random,95% CI
1 Sodium benzoate versus placebo					
Gonzalez 1994	0/7	0/9			Not estimable
Subtotal (95% CI)	**7**	**9**			**Not estimable**

Total events: 0 (Treatment), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: not applicable

2 Sodium benzoate versus lactulose/lactitol					
Sushma 1992	36/38	30/36		94.1 %	1.14 [0.96, 1.34]
Uribe 1990	12/48	15/60		5.9 %	1.00 [0.52, 1.93]
Subtotal (95% CI)	**86**	**96**		**100.0 %**	**1.13 [0.96, 1.32]**

0.01 0.1 1 10 100

Treatment   Control

(*Continued* . . .)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI

Total events: 48 (Treatment), 45 (Control)

Heterogeneity: Tau² = 0.0; Chi² = 0.14, df = 1 (P = 0.71); I² =0.0%

Test for overall effect: Z = 1.49 (P = 0.14)

3 Glycerol phenylbutyrate versus placebo

| Rockey 2014 | 71/90 | 67/88 | | 100.0 % | 1.04 [0.88, 1.21] |
| **Subtotal (95% CI)** | **90** | **88** | | **100.0 %** | **1.04 [0.88, 1.21]** |

Total events: 71 (Treatment), 67 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)

4 Ornithine phenylacetate versus placebo

STOP-HE 2017	47/116	39/115		75.1 %	1.19 [0.85, 1.67]
Ventura-Cots 2016	9/20	10/18		24.9 %	0.81 [0.43, 1.53]
Subtotal (95% CI)	**136**	**133**		**100.0 %**	**1.08 [0.78, 1.51]**

Total events: 56 (Treatment), 49 (Control)

Heterogeneity: Tau² = 0.01; Chi² = 1.12, df = 1 (P = 0.29); I² =11%

Test for overall effect: Z = 0.48 (P = 0.63)

5 Polyethylene glycol versus lactulose

Naderian 2017	0/21	0/19			Not estimable
Shehata 2018	16/49	22/48		100.0 %	0.71 [0.43, 1.18]
Subtotal (95% CI)	**70**	**67**		**100.0 %**	**0.71 [0.43, 1.18]**

Total events: 16 (Treatment), 22 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.31 (P = 0.19)

```
        0.01   0.1    1    10   100
            Treatment    Control
```

Review: Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis
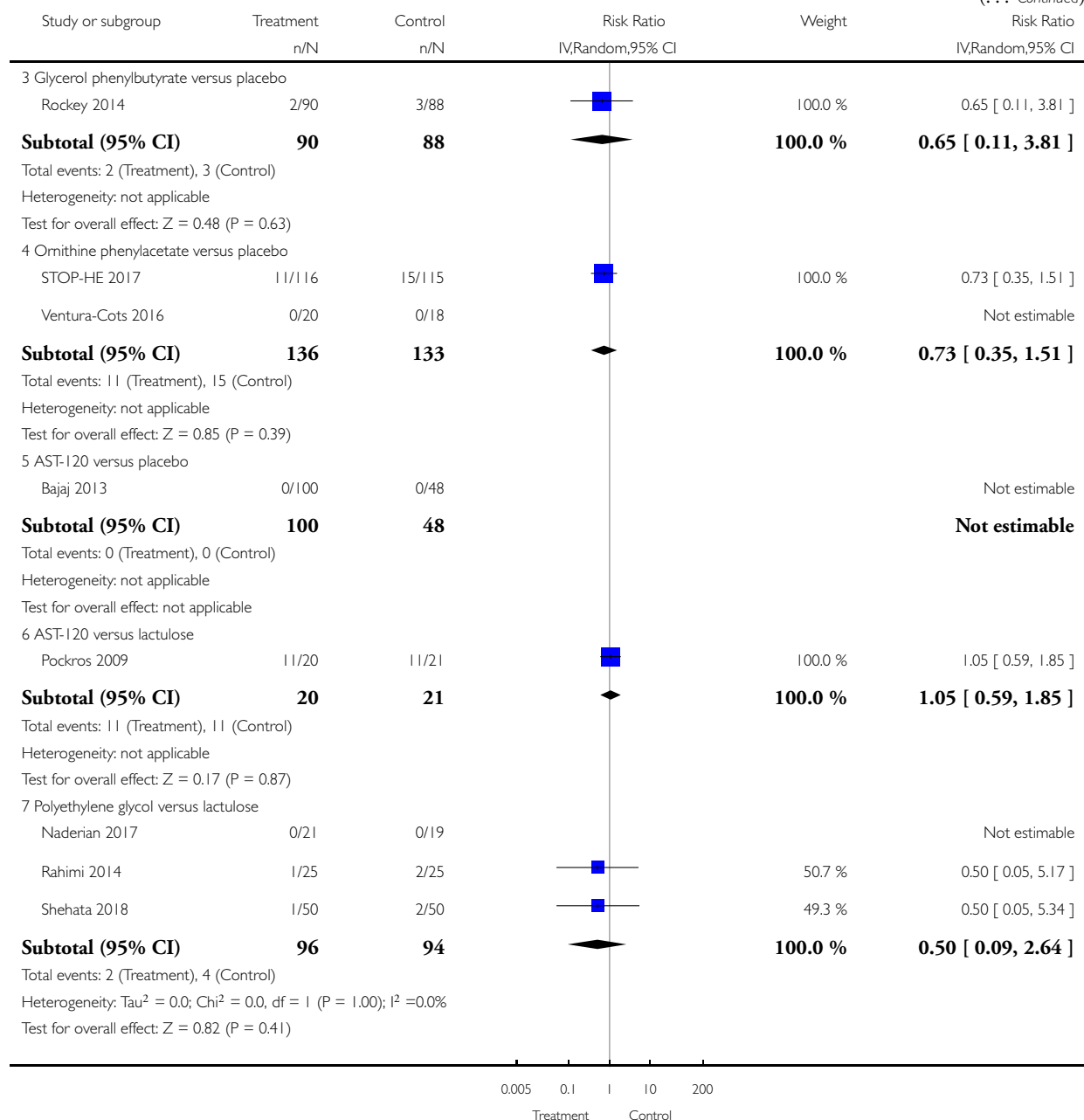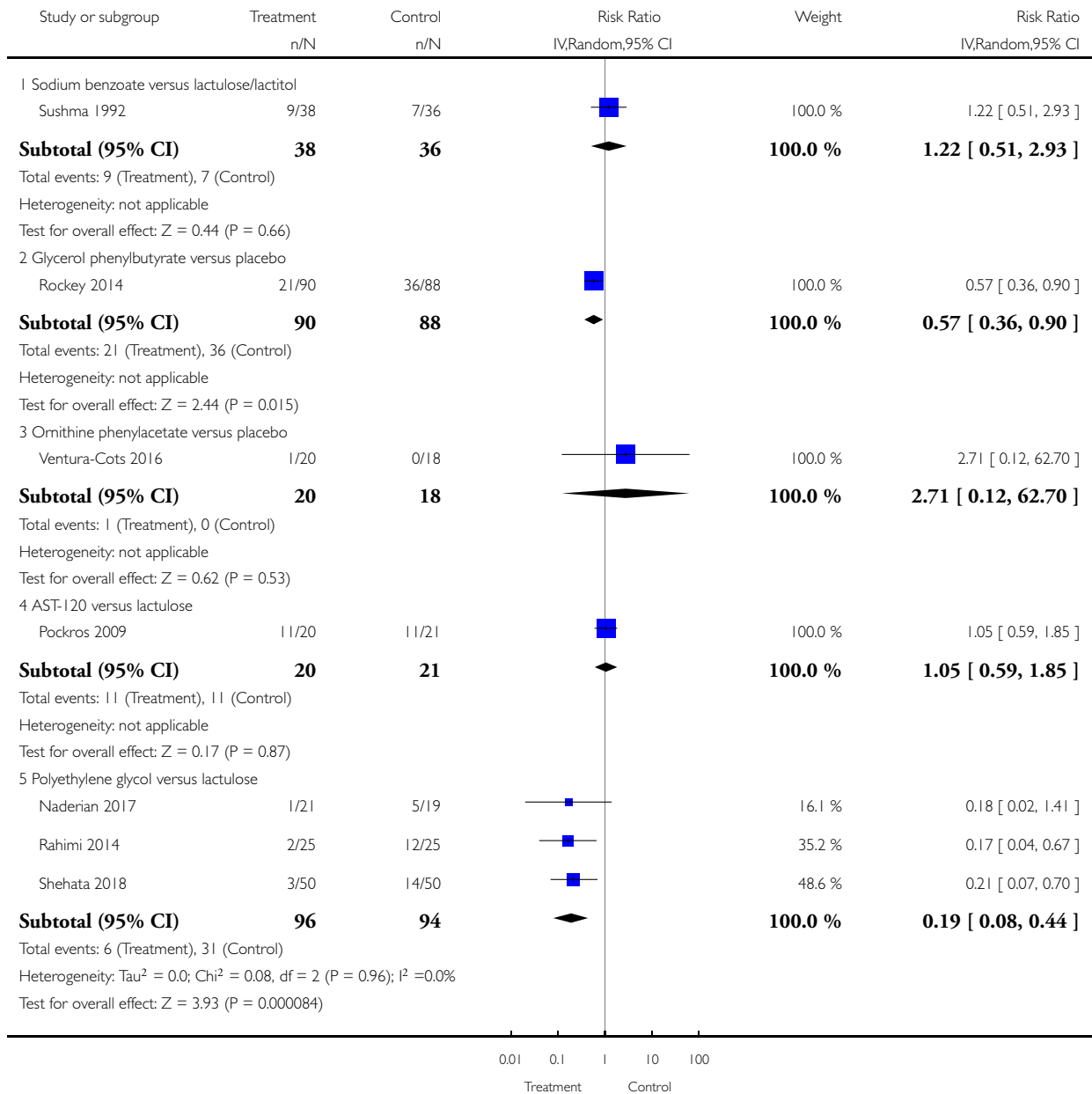
Comparison: 1 Pharmacotherapies that specifically target ammonia versus placebo, lactulose, or lactitol
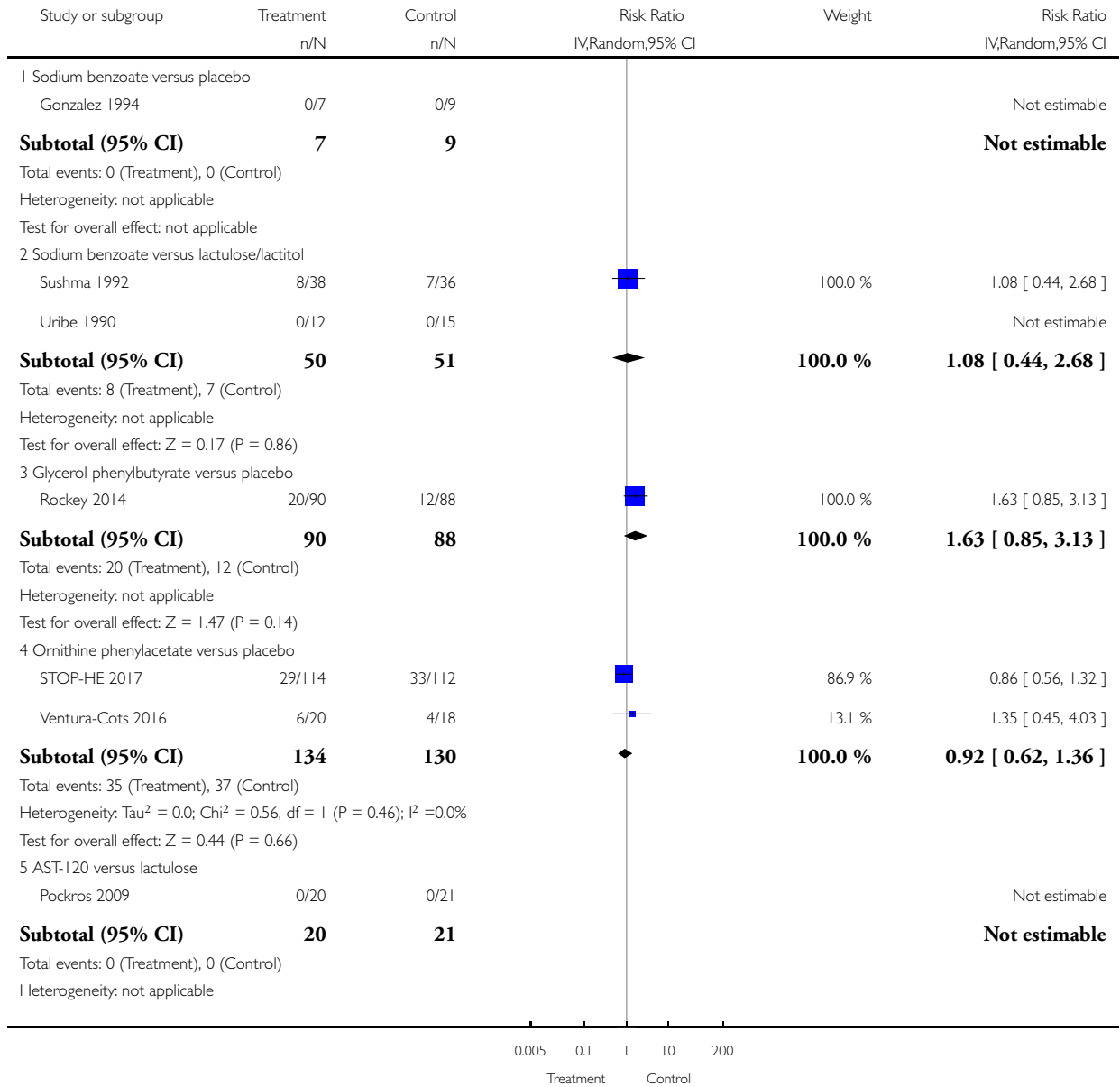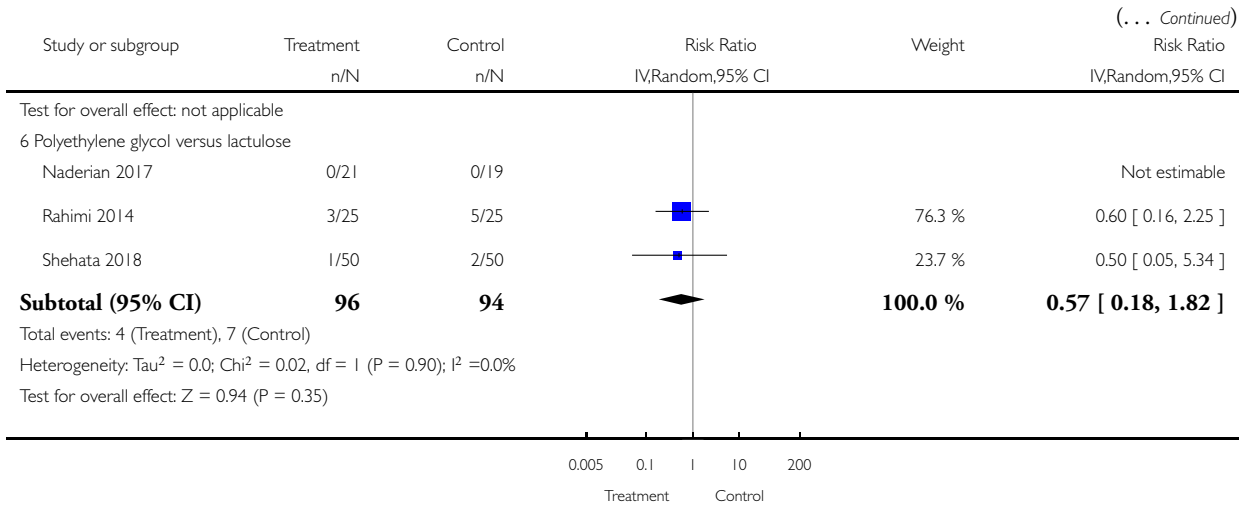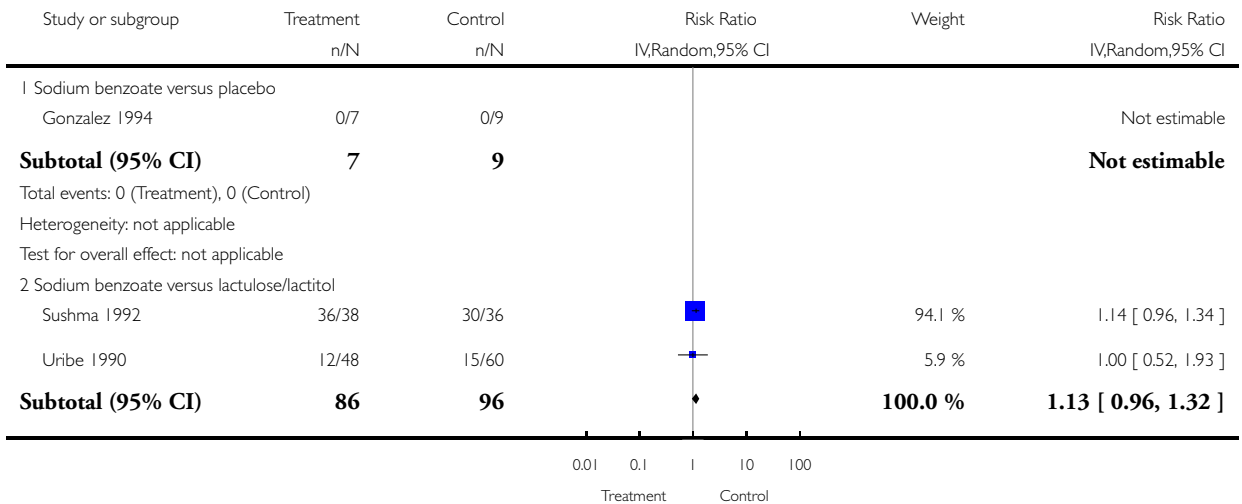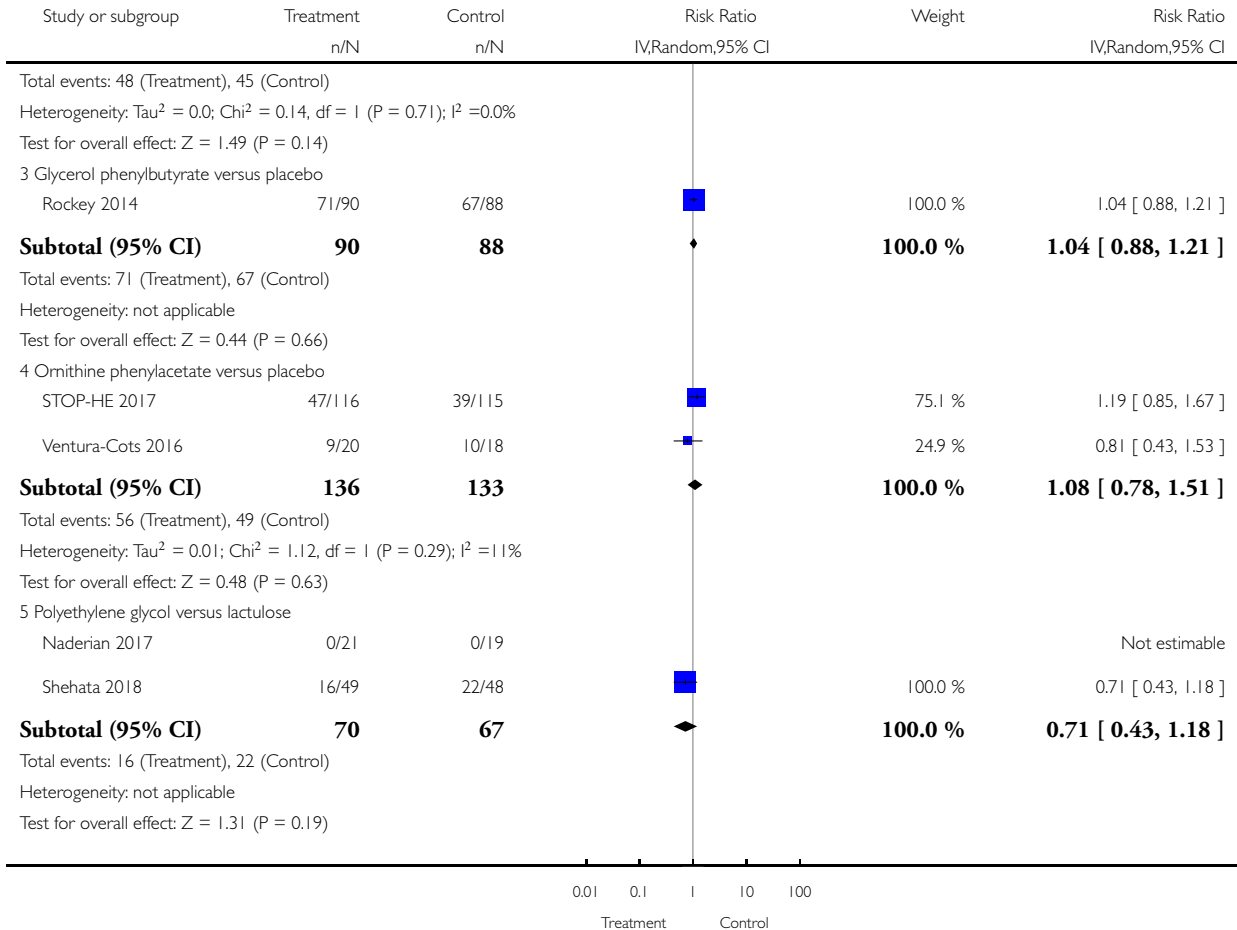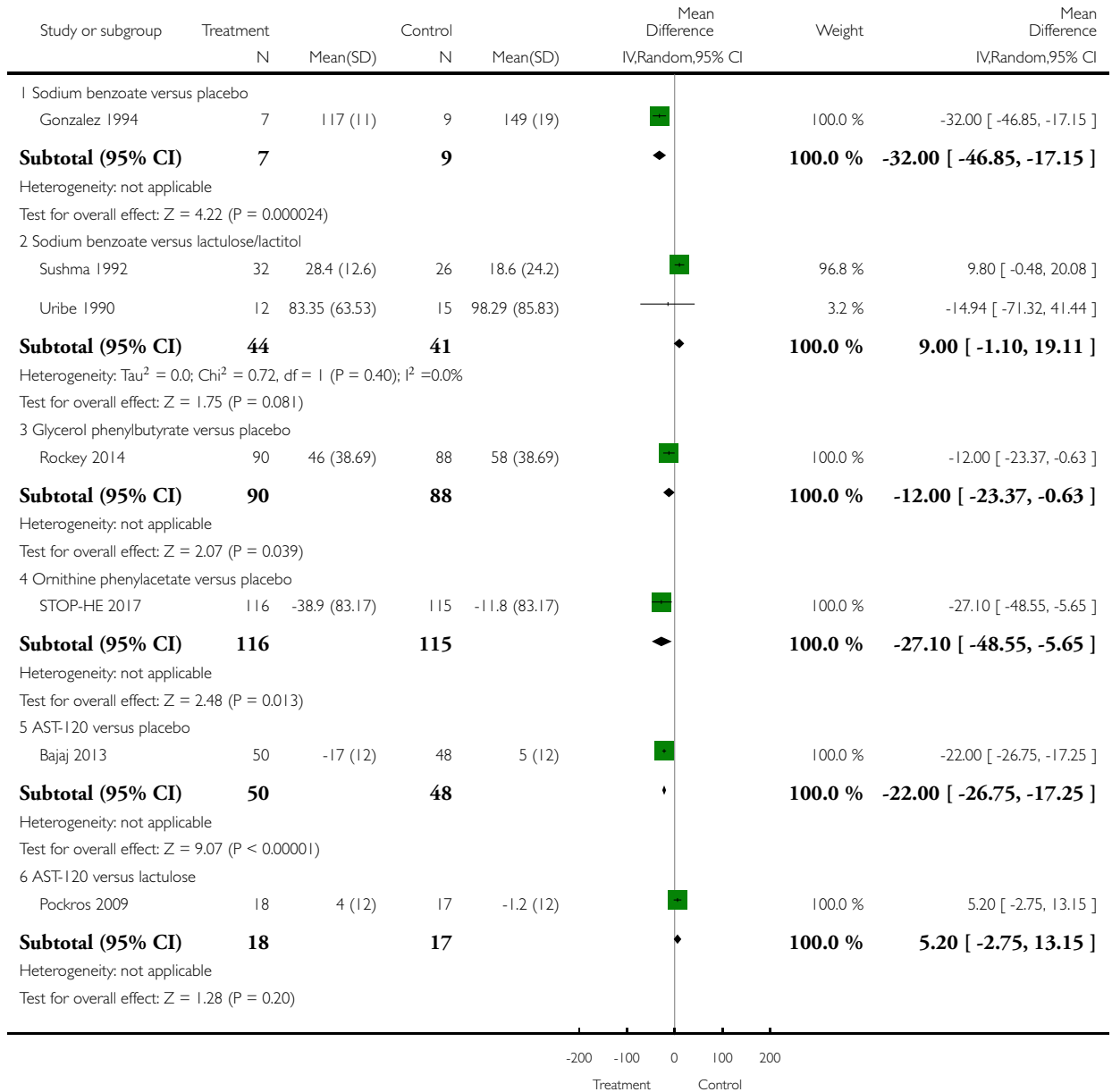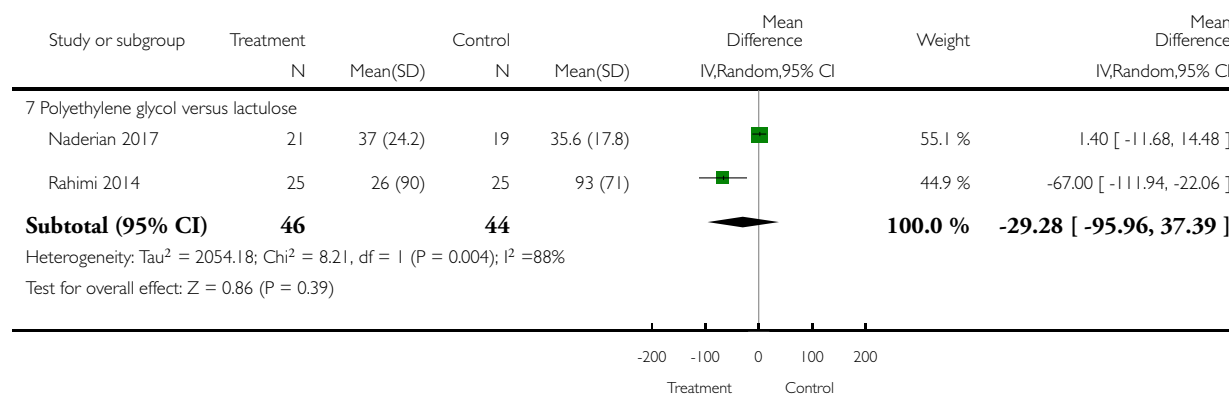
Outcome: 5 Ammonia

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Sodium benzoate versus placebo							
Gonzalez 1994	7	117 (11)	9	149 (19)		100.0 %	-32.00 [-46.85, -17.15]
Subtotal (95% CI)	**7**		**9**			**100.0 %**	**-32.00 [-46.85, -17.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.22 (P = 0.000024)							
2 Sodium benzoate versus lactulose/lactitol							
Sushma 1992	32	28.4 (12.6)	26	18.6 (24.2)		96.8 %	9.80 [-0.48, 20.08]
Uribe 1990	12	83.35 (63.53)	15	98.29 (85.83)		3.2 %	-14.94 [-71.32, 41.44]
Subtotal (95% CI)	**44**		**41**			**100.0 %**	**9.00 [-1.10, 19.11]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.72, df = 1 (P = 0.40); I^2 =0.0%							
Test for overall effect: Z = 1.75 (P = 0.081)							
3 Glycerol phenylbutyrate versus placebo							
Rockey 2014	90	46 (38.69)	88	58 (38.69)		100.0 %	-12.00 [-23.37, -0.63]
Subtotal (95% CI)	**90**		**88**			**100.0 %**	**-12.00 [-23.37, -0.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.07 (P = 0.039)							
4 Ornithine phenylacetate versus placebo							
STOP-HE 2017	116	-38.9 (83.17)	115	-11.8 (83.17)		100.0 %	-27.10 [-48.55, -5.65]
Subtotal (95% CI)	**116**		**115**			**100.0 %**	**-27.10 [-48.55, -5.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.48 (P = 0.013)							
5 AST-120 versus placebo							
Bajaj 2013	50	-17 (12)	48	5 (12)		100.0 %	-22.00 [-26.75, -17.25]
Subtotal (95% CI)	**50**		**48**			**100.0 %**	**-22.00 [-26.75, -17.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.07 (P < 0.00001)							
6 AST-120 versus lactulose							
Pockros 2009	18	4 (12)	17	-1.2 (12)		100.0 %	5.20 [-2.75, 13.15]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**5.20 [-2.75, 13.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.28 (P = 0.20)							

-200   -100   0   100   200

Treatment   Control

(*Continued* . . .)

Study or subgroup	Treatment		Control		Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	N	Mean(SD)	N	Mean(SD)			
7 Polyethylene glycol versus lactulose							
Naderian 2017	21	37 (24.2)	19	35.6 (17.8)		55.1 %	1.40 [-11.68, 14.48]
Rahimi 2014	25	26 (90)	25	93 (71)		44.9 %	-67.00 [-111.94, -22.06]
Subtotal (95% CI)	**46**		**44**			**100.0 %**	**-29.28 [-95.96, 37.39]**

Heterogeneity: Tau^2 = 2054.18; Chi^2 = 8.21, df = 1 (P = 0.004); I^2 =88%

Test for overall effect: Z = 0.86 (P = 0.39)

-200   -100   0   100   200

Treatment   Control

ADDITIONAL TABLES

Table 1. Pharmacotherapeutic agents that specifically target ammonia

Agent	Appearance	Doses used	Mechanisms of action
Sodium benzoate[a]	Crystalline powder	Given orally in solution: standard dose 10 g daily in divided doses	Conjugates with glycine to form hippurate, which is then excreted via the kidneys
Sodium phenylbutyrate[a]	Crystalline powder	Administered orally or via nasogastric tube; 200 mg/kg/day	Conjugates with glutamine to form phenylacetylglutamine (PAG) in the liver and kidneys, which is then eliminated in the urine. As glutamine is incorporated into PAG, more is synthesized by amidation of glutamic acid by ammonia through glutamine synthetase
Glycerol phenylbutyrate	Liquid	Administered orally, 6 mL twice daily for 16 weeks	Prodrug of sodium phenylbutyrate. Conjugates with glutamine to form phenylacetylglutamine (PAG) in the liver and kidneys, which is then eliminated in the urine. As glutamine is incorporated into PAG, more is synthesized by amidation of glutamic acid by ammonia through glutamine synthetase

Table 1. Pharmacotherapeutic agents that specifically target ammonia (*Continued*)

Sodium phenylacetate	Crystalline powder	Sodium phenylacetate is usually used in combination with sodium benzoate as adjunctive therapy for the treatment of acute hyperammonaemia and associated encephalopathy in people with urea cycle enzyme deficiencies. It is supplied as a solution containing 100 mg/mL of sodium phenylacetate and 100 mg/mL of sodium benzoate (Ammonul 10%/10%). It is administered as an IV infusion 5.5 g/m^2/day	Conjugates with glutamine to form phenylacetylglutamine (PAG) in the liver and kidneys, which is then eliminated in the urine. As glutamine is incorporated into PAG, more is synthesized by amidation of glutamic acid by ammonia through glutamine synthetase
Ornithine phenylacetate (OCR-002)	Crystalline salt	Administered as IV infusion 10 g/24 h (0.42 g/h)	Reduces ammonia through 2 pathways: - L-ornithine acts as a substrate for the synthesis of glutamine from ammonia in skeletal muscle; and, - phenylacetate and glutamine combines to form phenylacetylglutamine, which is excreted in the urine.
AST-120 (spherical carbon microsphere adsorbent)	Powder	Orally administered powder (sachets), 2 g three times daily	Differs structurally from activated charcoal and exhibits superior adsorptive capacity for certain organic compounds typically those with a low molecular weight < 10 kDa. It binds ammonia in the lumen of the lower gastrointestinal tract and facilitates its excretion
Polyethylene glycol (PEG)	Solution of 280 g of PEG in 4 L of water	Administered orally or via a nasogastric tube in a single 4 L dose over 20-30 min	A cathartic which causes rapid clearance of ammonia-synthesising gut bacteria from the gut lumen

IV: intravenous

[a] Includes relatively high amounts of sodium.

Table 2. Composite neurocognitive assessment tools

Assessment tool	Description	Advantages	Disadvantages
Portal-Systemic Encephalopathy Sum and Index (PSE Sum/PSE Index) (Conn 1977)	Provides an index of the severity of hepatic encephalopathy derived by adding scores for the degree of abnormality, expressed on a 0 to 4+ scale, for: • Mental status assessed using West Haven Criteria • Asterixis • Number Connection Test A time • Blood ammonia concentration • EEG mean cycle frequency Each component is arbitrarily weighted in proportion to its importance; mental state is weighted by a factor of 3, while the other variables are assigned a factor of 1 The PSE Sum is the total of the weighted scores; its maximum possible value is 28 The PSE Index is the ratio of the estimated PSE Sum to the maximum possible **Approximate time required:** dependent on the time taken to obtain the results of the blood ammonia and the EEG	• Comprehensive • Use of the PSE Index takes account of the eventuality that information on one or more of the components of the PSE Sum may not be available at every time point	• Time-consuming • EEG is often not readily available
Psychometric Hepatic Encephalopathy Score (PHES) (Weissenborn 2001)	**Format:** a battery of five pencil and paper tests **Aproximate time required:** 20 minutes **Domains tested:** • psychomotor speed • precision • visual perception • visuo-spatial orientation • visual construction • concentration • attention • memory	• Validated in several populations internationally • High diagnostic sensitivity and specificity • Multiple versions available to allow for repeated testing • Specifically designed to detect subtle cognitive changes in people with minimal hepatic encephalopathy	• Poor test of memory • Difficult to interpret and to score • Relies on fine motor skills • Unpopular in countries such as the USA due to lack of normative data and availability

Table 2. Composite neurocognitive assessment tools (*Continued*)

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1998)	A battery of tests that are also used to assess dementia, traumatic brain injury, stroke, multiple sclerosis and bipolar disorder. Recommended for use in the USA, where normative data is more widely available **Format:** a battery of pencil and paper tests **Approximate time required:** 25 minutes **Domains tested:** • immediate memory • delayed memory • attention • visuo-spatial ability • language	• Available in multiple languages • Multiple versions available to allow for repeated testing • Has USA-based norms	• Two domains are not affected in minimal hepatic encephalopathy • Difficult to interpret and to score • Relies on fine motor skills • Scarce data on sensitivity and specificity in hepatic encephalopathy
Hepatic Encephalopathy Scoring Algorithm (HESA) (Hassanein 2008)	An algorithm originally developed to assess the utility of extracorporeal albumin dialysis in the treatment of people with severe hepatic encephalopathy **Format:** a combination of clinical indicators and results from neurophysiological tests **Approximate time required:** 15 minutes **Domains tested:** • orientation • mental control • visuo-spatial memory • verbal memory • depression/anxiety • computation • attention • constructional ability	• Uses well-defined criteria • Simple and objective • Time-efficient • Able to identify low grades of hepatic encephalopathy more precisely • Thorough, so useful to grade hepatic encephalopathy in clinical trials	• Requires training of personnel to use • A long, labour-intensive test, so not widely used in clinical practice
Clinical Hepatic Encephalopathy Staging Scale (CHESS) (Ortiz 2007)	A scale from 0-9, designed to reduce interobserver variability **Format:** a set of nine questions that the observer must answer **Approximate time required:** 10 minutes **Domains tested:** • orientation • attention • language • consciousness	• Reflects the spectral nature of hepatic encephalopathy • Shows good consistency and reproducibility	• Not widely used apart from in clinical trials • Needs further validation

Table 2. Composite neurocognitive assessment tools *(Continued)*

Cognitive Drug Research (CDR) (Mardini 2008)	Developed in the UK specifically for people with minimal hepatic encephalopathy **Format:** computerized test consisting of a set of increasingly complex tasks based on yes/no responses. Seven tests with 50 parallel forms of each task **Approximate time required:** up to 30 minutes **Domains tested:** attention power and continuity, speed and quality of working and episodic memory	• Large normative data pool in the United Kingdom • Good correlation with the PHES test • High sensitivity and specificity • Multiple versions available to allow for repeated testing	• Time-consuming • Trail run needed before formal testing • Requires validation in other countries • Few data available for its use in people with cirrhosis

EEG: electroencephalogram

Table 3. Measurement of ammonia concentrations in the included trials

Trial	Type of blood sample	Unit measure	Time period for measurement differences
Gonzalez 1994	Venous	µg/dL	Baseline, 72 hours and 7 days
Sushma 1992	Arterial	µg/dL	Baseline, 72 hours and at recovery
Uribe 1990	Not specified	µg/dL	Baseline and 2 weeks
Rockey 2014	Venous	µmol/L*week	Measure based on the time normalised area under the time-concentration curve (TN-AUC$_{week}$)
STOP-HE 2017	Venous	µmol/L	Mean reduction in ammonia concentrations
Ventura-Cots 2016	Venous	µmol/L*120 hr	Measurement based on the time-normalized area under the curve time concentration curve (TN-AUC$_{0-120h}$)
Bajaj 2013	Venous	µg/dL	Baseline and 8 weeks
Pockros 2009	Venous	Not specified	Baseline and 4 weeks
Naderian 2017	Not specified	µmol/L	Reported as the mean difference from baseline to 24 hours
Rahimi 2014	Not specified	µmol/L	Reported as the mean difference from 6 to 24 hours

hr: hour

APPENDICES

Appendix 1. Search strategy

Database	Time span	Search terms
Cochrane Hepato-Biliary Controlled Trials Register	March 2019	((sodium and (benzoate or phenylacetate or phenylbutyrate)) or glycerol phenylbutyrate or ornithine phenylacetate or spherical carbon absorbant or activated charcoal or ammonul or buphenyl or ravicti or AST-120 or polyethylene* glycol or PEG or (ammoni* and scaveng*)) AND ((encephalopath* or HE) and cirrho*)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2019, Issue 3	#1 MeSH descriptor: [Phenylbutyrates] explode all trees #2 MeSH descriptor: [Phenylacetates] explode all trees #3 MeSH descriptor: [Sodium Benzoate] explode all trees #4 MeSH descriptor: [Charcoal] explode all trees #5 ((sodium and (benzoate or phenylacetate or phenylbutyrate)) or glycerol phenylbutyrate or ornithine phenylacetate or spherical carbon absorbant or activated charcoal or ammonul or buphenyl or ravicti or AST-120 or polyethylene* glycol or PEG or (ammoni* and scaveng*)) #6 #1 or #2 or #3 or #4 or #5 #7 MeSH descriptor: [Hepatic Encephalopathy] explode all trees #8 MeSH descriptor: [Fibrosis] explode all trees #9 #7 and #8 #10 ((encephalopath* or HE) and cirrho*) #11 #9 or #10 #12 #6 and #11
MEDLINE Ovid	1946 to March 2019	1. exp Phenylbutyrates/ or exp Phenylacetates/ or exp Sodium Benzoate/ 2. exp Charcoal/ 3. ((sodium and (benzoate or phenylacetate or phenylbutyrate)) or glycerol phenylbutyrate or ornithine phenylacetate or spherical carbon absorbant or activated charcoal or ammonul or buphenyl or ravicti or AST-120 or polyethylene* glycol or PEG or (ammoni* and scaveng*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 1 or 2 or 3 5. exp Hepatic Encephalopathy/ 6. exp Fibrosis/ 7. 5 and 6 8. ((encephalopath* or HE) and cirrho*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

		9. 7 or 8 10. 4 and 9
Embase Ovid	1974 to March 2019	1. exp benzoic acid/ 2. exp phenylacetic acid/ 3. exp 4 phenylbutyric acid/ 4. exp glycerol phenylbutyrate/ 5. exp ornithine phenylacetate/ 6. exp activated carbon/ 7. ((sodium and (benzoate or phenylacetate or phenylbutyrate)) or glycerol phenylbutyrate or ornithine phenylacetate or spherical carbon absorbant or activated charcoal or ammonul or buphenyl or ravicti or AST-120 or polyethylene* glycol or PEG or (ammoni* and scaveng*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. exp hepatic encephalopathy/ 10. exp liver cirrhosis/ 11. 9 and 10 12. ((encephalopath* or HE) and cirrho*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 13. 11 or 12 14. 8 and 13
LILACS (Bireme)	1982 to March 2019	((encephalopath$ or HE) and cirrho$) [Words] and ((sodium and (benzoate or phenylacetate or phenylbutyrate)) or glycerol phenylbutyrate or ornithine phenylacetate or spherical carbon absorbant or activated charcoal or ammonul or buphenyl or ravicti or AST-120 or polyethylene$ glycol or PEG or (ammoni$ and scaveng$)) [Words]
Science Citation Index Expanded (Web of Science)	1900 to March 2019	#3 #2 AND #1 #2 TS=((encephalopath* or HE) and cirrho*) #1 TS=((sodium and (benzoate or phenylacetate or phenylbutyrate)) or glycerol phenylbutyrate or ornithine phenylacetate or spherical carbon absorbant or activated charcoal or ammonul or buphenyl or ravicti or AST-120 or polyethylene* glycol or PEG or (ammoni* and scaveng*))
Conference Proceedings Citation Index - Science (Web of Science)	1990 to March 2019	#3 #2 AND #1 #2 TS=((encephalopath* or HE) and cirrho*) #1 TS=((sodium and (benzoate or phenylacetate or phenylbutyrate)) or glycerol phenylbutyrate or ornithine phenylacetate or spherical carbon absorbant or activated charcoal or ammonul or buphenyl or ravicti or AST-120 or polyethylene* glycol or PEG or (ammoni* and scaveng*))

WHAT'S NEW

Date	Event	Description
10 July 2019	Amended	Adjustment to the number of trials at low risk of bias following removal of the 'For-profit bias' category The units of ammonia measurements provided A table is added, specifying details of the ammonia measurements in the included trials

HISTORY

Protocol first published: Issue 8, 2016

Review first published: Issue 6, 2019

Date	Event	Description
30 June 2019	Amended	Sumary of Findings tables amalgamated

CONTRIBUTIONS OF AUTHORS

HDZ drafted the review, and identified and selected trials, conducted the data extraction, analyses and interpretation of the results. APZ identified and selected trials and assisted with the data extraction. LLG and MYM identified and selected trials, contributed to the analyses and interpretation of the results, and revised the review.

All authors participated in the final revision of the review and have approved of the submitted version.

DECLARATIONS OF INTEREST

Harry Zacharias: none

Antony Zacharias: none

Lise L Gluud: none

Marsha Y Morgan: none

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Internal sources

- No funding, Other.

External sources

- No funding, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title to more precisely reflect the modes of action of the interventions included in the review and to make it clear that we only included adult participants, and we changed the wording of the review objectives to reflect the changes we had made to the title. We also updated the methods according to the current recommendations of Cochrane Hepato-Biliary. The updates include changes to the wording of the 'Risk of bias' assessment; obligatory inclusion of observational studies for the assessment of adverse events; and searching of the LILACS database. We did not include liver-related mortality as a secondary outcome as most trials do report this separately. We upgraded blood ammonia from an exploratory to a secondary outcome as these pharmacotherapies specifically target ammonia. There were insufficient data to include Number Connection Test results as an exploratory outcome. We did not undertake subgroup analyses because the number of randomised clinical trials identified was too small. We did not undertake sensitivity analyses because the outcome data sets were complete in the intervention and control groups in all of the included trials. We did not undertake Trial Sequential Analyses because the number of events, participants, and trials was insufficient.