Treatment of hepatic encephalopathy – systematic Cochrane reviews of randomised clinical trials

PhD Thesis

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Preface/Acknowledgements

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Original papers

This PhD thesis is based on the following papers:

1. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004;328:1046-50.[55]

2. Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.[56]

3. Als-Nielsen B, Koretz R, Kjaergard LL, Gluud C. Branched-chain amino acids for acute and chronic hepatic encephalopathy. In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.[57]

4. Als-Nielsen B, Gluud LL, Gluud C. Dopaminergic agents for hepatic encephalopathy (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2004. Chichester, UK: John Wiley & Sons, Ltd.[58]

5. Kjaergard LL, Liu J, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. *JAMA* 2003;289:217-22.[60]

Abstract

Objectives To assess the effects of non-absorbable disaccharides (lactulose and lactitol), benzodiazepine receptor antagonists (flumazenil), branched-chain amino acids, dopaminergic agonists, and liver support systems in patients with hepatic encephalopathy.

Methods Systematic reviews of relevant randomised trials. Trials were identified through The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Library, MEDLINE, EMBASE, manual searches of bibliographies and journals, authors of trials, and pharmaceutical companies. We used meta-analysis based on a random effects model to determine intervention effects on hepatic encephalopathy, all-cause mortality and adverse effects. We performed subgroup analyses with regard to methodological quality and type of hepatic encephalopathy.

Results Overall, non-absorbable disaccharides and branched-chain amino acids seemed to improve patients with cirrhosis and hepatic encephalopathy, but this effect was only seen in low-quality trials and may reflect bias. Non-absorbable disaccharides were statistically inferior to antibiotics on improvement of hepatic encephalopathy, but it is uncertain whether antibiotics should be used for hepatic encephalopathy in clinical practice. Flumazenil caused short-term improvement of hepatic encephalopathy in patients with cirrhosis, but the duration of this effect and the impact on the course of hepatic encephalopathy are uncertain. Flumazenil had no significant effect on mortality and may be associated with adverse events. Dopaminergic agonists had no significant beneficial effects in patients with acute liver failure or cirrhosis and hepatic encephalopathy. Liver support systems caused improvement of hepatic encephalopathy in patients with acute or acute-on-chronic liver failure. However, support systems did not significantly reduce mortality and may be associated with adverse events.

Conclusions We did not find reliable evidence of benefit of the assessed treatments used in patients with hepatic encephalopathy. The clinical intervention research on hepatic encephalopathy is flawed by major limitations. None of the treatments can be recommended for general use in clinical practice.

Dansk resumé

Introduktion Formålet var at vurdere effekten af nonabsorberbare disakkarider (lactulose og lactitol), benzodiazepinantagonister (flumazenil), forgrenede aminosyrer, dopaminerge agonister, og levererstatningssystemer i behandlingen af patienter med hepatisk encefalopati.

Materialer og metoder Systematiske oversigter af relevante randomiserede forsøg. Vi fandt forsøg gennem Cochrane Hepato-Biliær Gruppens register over randomiserede forsøg, Cochrane-biblioteket, MEDLINE og EMBASE samt korrespondance med eksperter og medicinalindustrien. Vi benyttede meta-analyse baseret på en *random effects* model for at vurdere behandlingseffekterne på hepatisk encefalopati, død og bivirkninger. Vi foretog planlagte subgruppeanalyser, hvor vi stratificerede forsøg efter kvalitet og typen af hepatisk encefalopati.

Resultater Samlet set syntes nonabsorberbare disakkarider og forgrenede aminosyrer, at forbedre tilstanden hos patienter med cirrose og hepatisk encefalopati, men denne effekt sås kun i lavkvalitetsforsøg og kan afspejle bias. Nonabsorberbare disakkarider var statistisk signifikant dårligere end antibiotika til at forbedre hepatisk encefalopati, men det er usikkert om antibiotika bør anvendes til hepatisk encefalopati i klinisk praksis. Flumazenil førte til kortvarig forbedring af hepatisk encefalopati i patienter med cirrose, men det er uvist hvor længe denne effekt varer eller om flumazenil påvirker patientens samlede forløb. Flumazenil havde ingen signifikant effekt på overlevelse og kan være associeret med bivirkninger. Dopaminerge agonister havde ingen signifikant effekt på patienter med akut leversvigt eller patienter med cirrose og hepatisk encefalopati. Levererstatningssystemer forbedrede symptomerne på hepatisk encefalopati hos patienter med akut leversvigt, men havde ingen signifikant effekt på overlevelse og kan være associeret med bivirkninger.

Diskussion Vi fandt ikke pålidelig evidens for gavn af de undersøgte behandlinger til patienter med hepatisk encefalopati. Den kliniske interventionsforskning indenfor hepatisk encefalopati er begrænset af fundamentale svagheder. Ingen af behandlingerne kan anbefales til generel kliniske brug.

Introduction

Hepatic encephalopathy is a complex neuropsychiatric syndrome, which may complicate acute or chronic liver failure.[1] It is characterised by changes in mental state including a wide range of neuropsychiatric symptoms ranging from minor not readily discernible signs of altered brain function to deep coma.[2] Due to the wide spectrum of symptoms and underlying liver failure, hepatic encephalopathy has traditionally been divided into several categories. Unfortunately, the terminology is confusing and not logically consistent, which has led to major discrepancies and controversies among specialists.[3]

In patients with chronic liver failure the symptoms of hepatic encephalopathy has traditionally been classified as acute, chronic, and minimal.[4] Acute encephalopathy involves an abrupt onset of neuropsychiatric symptoms in patients with chronic liver disease. The encephalopathy may be idiopathic or precipitated by e.g. infection, gastrointestinal bleeding, electrolyte disturbance, constipation, medication, renal dysfunction, or alcohol withdrawal. Chronic hepatic encephalopathy involves persistent neuropsychiatric dysfunction in patients with chronic liver disease. The onset is usually insidious and the dysfunction may be clinically overt (i.e., chronic hepatic encephalopathy) or only demonstrable by psychometric testing (i.e., minimal hepatic encephalopathy also known as latent or subclinical encephalopathy).

In patients with acute liver failure, hepatic encephalopathy has not been classified into different categories.[4] Acute liver failure has, however, traditionally been categorised according to whether it occurs in patients without pre-existing liver disease (acute liver failure) or in patients with chronic liver disease (acute-on-chronic liver failure).[5, 6]

Due to the inconsistency and overlap of terminology (e.g., acute hepatic encephalopathy in patients with chronic liver failure and hepatic encephalopathy associated with acute-on-chronic liver failure), a Working Party has recently published a consensus report on definition and classification of hepatic encephalopathy.[3] In short, they classify hepatic encephalopathy as type A, type B and type C. Type A (for acute) is encephalopathy associated with acute liver failure. Type B (for bypass) is related to those unusual patients whose portal circulation bypasses a healthy liver. Type C (for cirrhosis) is

encephalopathy associated with cirrhosis and portal hypertension/or portalsystemic shunts.[3]

It is estimated that about 95% of all incidences of hepatic encephalopathy occur in patients with cirrhosis.[7] Although the prevalence of hepatic encephalopathy is not well known, minor signs of altered brain function has been reported to be present in at least 50-70% of patients with cirrhosis.[8-11] The occurrence of hepatic encephalopathy in patients with cirrhosis is associated with poor survival: 42% at one year[12] and 16% - 22%[13, 14] at five years. Cirrhosis was the 12th leading cause of death in the US in 2000, accounting for more than 25.000 deaths.[15] In Denmark, hepato-biliary diseases accounted for 1035 deaths in 2000, the majority being due to cirrhosis.[16]

Pathogenesis

Hepatic encephalopathy is reversible and can exhibit a fluctuating course. If the underlying liver dysfunction improves or if the liver is replaced by a functioning liver transplant, the symptoms of hepatic encephalopathy will improve or disappear. With regard to acute hepatic encephalopathy, an intervention directed against the precipitating cause(s) will lead to improvement or disappearance of acute hepatic encephalopathy. This reversibility suggests that hepatic encephalopathy is a metabolic problem secondary to liver dysfunction, but the pathogenesis is unknown.[1]

Traditionally, hepatic encephalopathy has been considered secondary to the accumulation of a toxic agent, which has not been metabolised by the liver.[1] For several years, it was debated whether the accumulation lead to brain energy failure or to selective disturbance of neurotransmission. Recent research points at an abnormal interaction between the altered astrocyte and other cellular elements.[17] This leads to low grade cerebral edema, which is accompanied by alterations in glioneural communication.[17, 18]

The nature of the circulating toxic agents responsible for hepatic encephalopathy has been a controversial issue since the 1970s. Several hypotheses based on different toxins have been suggested (Table 1). Gut-derived nitrogenous substances, in particular

ammonia, are acknowledged to play a major role in the pathogenesis.[19] Ammonia is released from several tissues (kidney, muscle), but its highest levels can be found in the portal vein.[20] Portal ammonia is derived from both the urease activity of colonic bacteria and the deamidation of glutamine in the small bowel. Ammonia is efficiently converted into urea in the healthy liver with a first pass hepatic clearance of around 80%.[20] In acute and chronic liver disease, increased arterial levels of ammonia are commonly seen. In liver failure, elevated arterial levels have been associated with an increased risk of cerebral herniation.[21] In chronic liver disease (cirrhosis) a more modest increase in arterial ammonia concentrations have been shown.[22] The blood-brain barrier permeability to ammonia is increased in patients with hepatic encephalopathy,[23] but the plasma ammonia levels have been shown to correlate poorly with the severity of hepatic encephalopathy.[24]

Table 1. Circulating toxins and suggested hypotheses for their role in the pathogenesis of hepatic encephalopathy

1. Ammonia
• Astrocyte swelling through influx of glutamine
2. Synergistic toxins
• Mercaptans, phenols, and short-chain fatty acids may exacerbate the effects of ammonia on the brain
3. Endogenous benzodiazepines
• Bind to the GABA/benzodiazepine complex resulting in neural inhibition
4. False neurotransmitters
• Imbalance between increased aromatic amino acids and decreased branched-chain amino acids favours the entrance of the former into the brain. The aromatic amino acids may then be metabolised to false neurotransmitters
5. Manganese
• Accumulation in basal ganglia may impair dopaminergic neurotransmission
6. Cytokines
• Mediators of inflammation (TNF-α, IL-Iβ, IL-6) may exacerbate the effects of ammonia on the brain

Other gut-derived toxins have been proposed (Table 1). Products of colonic bacterial metabolism, such as mercaptans, phenols, and short-chain fatty acids may potentiate the assumed toxic ammonia effects in the brain.[25] Accumulation of endogenous benzodiazepines may bind to the γ-aminobutyric acid-benzodiazepine complex resulting in neural inhibition.[26-28] The false neurotransmitter hypothesis suggests that hepatic encephalopathy is caused by a derangement in the balance of amino acids in the plasma.[29] Brain neurotransmitter synthesis is regulated by the central nervous system

concentration of precursor amino acids. An imbalance between increased plasma aromatic amino acids and decreased branched-chain amino acids favours the entrance of the former into the brain. The aromatic amino acids may then be metabolised to false neurotransmitters (octopamine and phenylethanolamine).[30] Manganese may deposit in basal ganglia and induce extrapyramidal symptomatology.[31] Recent studies indicate that mediators of inflammation (tumor necrosis factor-alpha (TNF-α), interleukin-I beta (IL-Iβ), interleukin-6 (IL-6)) may exacerbate the effects of ammonia on the brain.[32]

At present researchers are turning away from the idea of 'one toxic agent' and embracing that the suggested toxins may contribute in combination or in synergistic ways to the very varied symptomatology of hepatic encephalopathy.[33]

Treatment

Understanding the pathophysiology of a disease is essential to develop effective treatments, although relying on pathophysiology can lead to fallacious treatments.[34] The unknown pathogenesis of hepatic encephalopathy makes it difficult to find effective treatments, although some treatments have proven very effective before the pathophysiological mechanism were known, e.g., citrus fruit for scurvy.[35]

Treatment of hepatic encephalopathy aims at three major goals: treating precipitating factors, reducing the production and absorption of ammonia, and counteracting abnormalities of central neurotransmission.

The treatment of precipitating factors such as gastrointestinal bleeding, infection, electrolyte disturbance, and constipation has never been formally tested, but is based on clinical experience. It would seem difficult and maybe unethical to assess in randomised trials whether treatment of precipitating factors (e.g., treatment of bleeding) also have an impact on the symptoms of hepatic encephalopathy.

Randomised trials are needed to assess the multiple treatments suggested for hepatic encephalopathy (Table 2). Protein restriction was introduced in the 1950s to treat hepatic encephalopathy.[36] Despite the lack of evidence[37] and advice from experts[38-40]

physicians still recommend[41] and use protein restriction in the treatment of hepatic encephalopathy.[42] Non-absorbable disaccharides are the first line pharmacological treatment for hepatic encephalopathy.[43] Antibiotics can be considered a therapeutic alternative to non-absorbable disaccharides in acute hepatic encephalopathy. In chronic encephalopathy antibiotics should be reserved for patients who respond poorly to non-absorbable disaccharides. Flumazenil, a benzodiazepine-receptor antagonist, may be used in selected patients where benzodiazepine use is suspected. Oral branched-chain amino acids may be considered for patients intolerant of protein. Bromocriptine is indicated for patients with chronic encephalopathy unresponsive to other therapy.[43] Both L-ornithine-L-aspartate and sodium benzoate are considered experimental treatments. They are not registered in the US, but preliminary results are encouraging.[43] Liver support systems may 'bridge' patients with severe liver failure to transplantation or recovery.[44] Liver transplantation is the preferred treatment in a range of acute and chronic end stage liver disorders.[45]

Table 2. Principles of suggested treatments for patients with hepatic encephalopathy

1.	Treatment of precipitating factors
2.	Reduction of the production and absorption of ammonia
	• Protein restriction
	• Non-absorbable disaccharides (lactulose and lactitol)
	• Antibiotics
	• L-ornithine-L-aspartate
	• Sodium benzoate
3.	Counteract abnormalities of central neurotransmission
	• Flumazenil
	• Branched-chain amino acids
	• Dopaminergic agents (e.g., bromocriptine)
4.	Removal of substances from the blood
	• Liver support systems
5.	Liver transplantation

The beneficial and harmful effects of the multiple treatments used for hepatic encephalopathy have never been systematically assessed. There is an increasing demand within the health care system to provide evidence of the efficacy of treatments. In order to ensure patients the best possible treatments and to implement rational allocation of resources, evidence-based medicine has received increasing attention to provide evidence to both guidelines for clinical practice[46] and health care decision making.[47]

Evidence-based medicine can be described as the conscientious use of the best research evidence in clinical decision making.[48] With evidence-based medicine, the paradigm shifts from 'doing what seems best,' relying on clinical experience and knowledge of pathophysiology, to 'knowing what is likely to be best,' relying on the best available research evidence. The best research evidence is that associated with the smallest risk of systematic error (bias) and random error which give the most reliable results. Choosing the best research evidence depends on the clinical questions asked. Certain study designs are superior to others when answering particular questions.[48, 49] When it comes to assessing whether a treatment does more good than harm, a hierarchy of evidence has been developed to help evidence-based practitioners navigate the maze of clinical research.[50] The construction of the hierarchy of evidence is mainly based on the risk of systematic and random errors associated with different research designs.[51] Randomised trials and systematic reviews of randomised trials are placed at the top of the hierarchy, due to their ability to control bias.[46]

Table 3. Categories of evidence regarding the effects of interventions

1a	Evidence from meta-analysis of randomised controlled trials
1b	Evidence from at least one randomised controlled trial
2a	Evidence from at least one controlled study without randomisation
2b	Evidence from at least one other type of quasi-experimental study
3	Evidence from descriptive studies, such as comparative studies, correlation studies, and case-control studies
4	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Objectives

The objectives were to assess the beneficial and harmful effects of the following interventions for patients with acute, chronic or minimal hepatic encephalopathy, or encephalopathy associated with acute liver failure:

1. Non-absorbable disaccharides (lactulose and lactitol).
2. Benzodiazepine receptor antagonists (e.g., flumazenil).
3. Branched-chain amino acids.
4. Dopaminergic agents (e.g., bromocriptine).
5. Liver support systems.

Methods

All reviews were performed according to published protocols following the recommendations of the Cochrane Reviewers' Handbook[52] and the QUOROM statement.[53]

Searching

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Library, MEDLINE, and EMBASE using the search strategies specified in the individual reviews.[54-60] We screened bibliographies of relevant articles and conference proceedings and wrote to experts and pharmaceutical companies.

Selection

We included all randomised trials comparing the treatments mentioned below. Inclusion was regardless of publication status, language, or blinding. Included patients had hepatic encephalopathy in connection with acute or chronic liver disease.

1a. Lactulose or lactitol versus no intervention or placebo.

1b. Lactulose or lactitol versus antibiotics.

2. Benzodiazepine receptor antagonists versus placebo or no intervention.
3. Branched-chain amino acids versus no nutritional support, placebo support, isocaloric support, isonitrogenous support, or other interventions with a potential effect on hepatic encephalopathy (e.g., lactulose or neomycin).
4. Dopaminergic agonists (e.g., levodopa or bromocriptine) versus placebo or no intervention.
5. Liver support systems versus standard medical care.

Validity assessment

At least two reviewers independently assessed the methodological trial quality[61-64] by examining three components: allocation sequence generation (classified as adequate if

based on computer-generated random numbers, table of random numbers, or similar), allocation concealment (classified as adequate if based on central randomisation, sealed envelopes, or similar), and blinding (classified as adequate if the trial was described as double blind or had blinded outcome assessment). We classified trials with adequate allocation concealment and adequate blinding as high quality.

Data abstraction

At least two reviewers independently extracted data from each trial. Our outcome measures were number of patients without improvement of hepatic encephalopathy, all-cause mortality, and adverse events. Improvement was defined as partial or complete resolution of clinical or subclinical symptoms of hepatic encephalopathy. All outcomes were assessed at the end of treatment and maximum follow-up.

Trial characteristics

We extracted the type and cause of the underlying liver disease, type of hepatic encephalopathy (acute, chronic, minimal, or associated with acute liver failure); mean age; proportion of men; number of patients randomised to each intervention arm; type, dose and duration of therapy; mode of administration; trial quality[61, 62]; trial design (parallel or cross-over); duration of follow-up; and number of patients excluded from analysis. We sought data on all patients irrespective of compliance or follow-up. Primary investigators were contacted if data were missing.

Quantitative data synthesis

All analyses were performed on the basis of intention to treat, including all randomised patients irrespective of compliance or follow up. If patients had missing outcome data, we carried forward the last reported observed response.[65] Data from the first period of cross-over trials were included. In four reviews,[54-60] binary outcomes were expressed as relative risks (RR) and in one review[56] as risk difference (RD), all with 95% confidence intervals (CI). We used a random effects model[66] because we anticipated clinical variability between trials. Statistical heterogeneity was explored by the chi-squared test with significance set at $P < 0.1$. The percentage of variation between trial results that is due to heterogeneity rather than chance was measured by I^2.[67] Potential sources of

heterogeneity were explored through subgroup analyses with regard to the methodological quality and type of hepatic encephalopathy. We used the test of interaction[68] to compare the difference between the estimates of subgroup analyses. Analyses were performed in Review Manager (latest version 4.2.7) for Windows and SPSS® (latest version 11.0) for Windows.

Results

Non-absorbable disaccharides

Figure 1 summarises the literature search. Twenty-two trials assessing lactulose or lactitol versus placebo, no treatment, or antibiotics were included.[69-90] Eighteen trials used a parallel group design and four a cross-over design. All trials were described as randomised, but adequate generation of the allocation sequence was only reported in four trials.[71, 81, 82, 90] Treatment allocation was adequately concealed in 10 trials.[69-72, 75, 79-81, 87, 90] Double blinding was reported in 15 trials,[69-74, 76, 79-81, 83-85, 87, 89, 90] and one trial had blinded outcome assessment.[30] We classified nine trials as high quality.[69-72, 79-81, 87, 90]

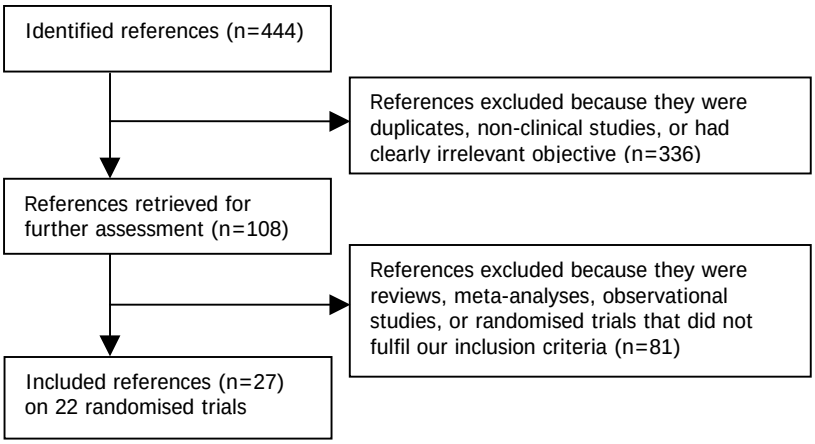

Figure 1. Selection process of eligible randomised trials on non-absorbable disaccharides from all identified references

Lactulose or lactitol versus placebo or no intervention

Description of trials

Ten trials with 280 patients (75% men) assessed lactulose or lactitol versus placebo or no intervention.[69-78] All patients had cirrhosis and acute,[74] chronic,[69, 71-73] acute or

chronic,[70] or minimal hepatic encephalopathy.[75-78] Eight trials assessed oral lactulose,[69-73, 75, 77, 78] one trial oral lactitol,[76] and one trial lactitol enemas.[74] The daily mean dosages of lactulose ranged from 30 g to 84 g (median 50 g). In six trials the dose was adjusted to obtain 2-3 semisoft stools per day. The median duration of treatment was 15 days (range 5 to 360 days). None of the trials followed patients after the end of treatment.

Meta-analyses

Compared with placebo or no intervention, lactulose and lactitol appeared to reduce the risk of no improvement of hepatic encephalopathy (RR 0.62, 95% CI 0.46 to 0.84, 6 trials; fig 2). This result was not robust to our subgroup analyses. High-quality trials found no significant effect of lactulose or lactitol (RR 0.92, 95% CI 0.42 to 2.04, 2 trials; fig 2), whereas low-quality trials found a significant beneficial effect of lactulose or lactitol (RR 0.57, 95% CI 0.40 to 0.83, 4 trials; fig 2). The difference in treatment response was, however, not statistically significant (P = 0.3 by test of interaction) and trial results were not significant heterogeneous, but the analyses had low power to detect differences.

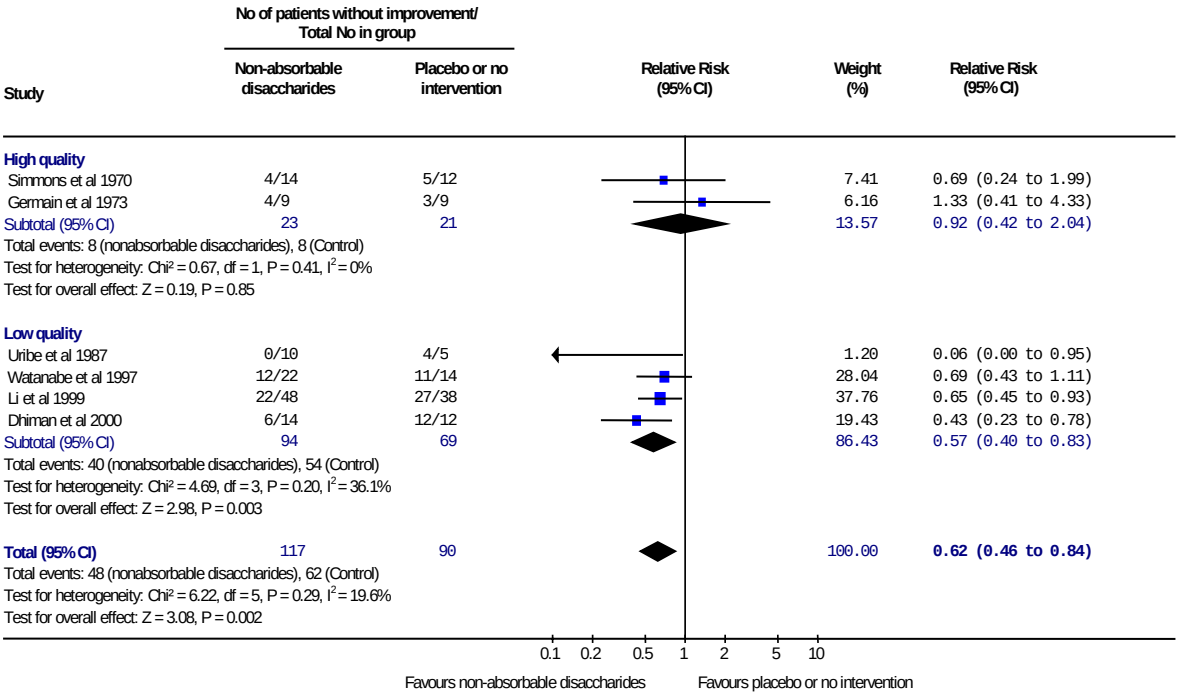

Figure 2. Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus placebo or no intervention, stratified according to quality of methods

However, the control group event rate was significantly associated with methodological quality (high-quality trials: 37% (95% CI 18 to 57%), low-quality trials: 75% (95% CI 64 to 85%); P = 0.02 by test of interaction). The event rate in the experimental group was not significantly different in trials with high (34%, 95% CI 15-53%) and low (44%, 95% CI 35-54%) quality (P = 0.4 by test of interaction). The treatment responses in acute, chronic, and minimal hepatic encephalopathy did not differ significantly. However, there was no statistically significant effect of lactulose or lactitol on acute (RR 0.27, 95% CI 0.02 to 3.28, 2 trials) or chronic hepatic encephalopathy (RR 1.33, 95% CI 0.41 to 4.33, 1 trial). Trials in patients with minimal hepatic encephalopathy found that lactulose or lactitol significantly reduced the risk of no improvement assessed by various psychometric tests (RR 0.61, 95% CI 0.47 to 0.79, 3 trials). These trials were all of low quality.

Compared with placebo or no intervention, lactulose and lactitol had no statistically significant effect on mortality (RR 0.41, 95% CI 0.02 to 8.68, 4 trials). Data on adverse events were incompletely reported. The majority only mentioned adverse events associated with non-absorbable disaccharides. We were therefore unable to perform a reliable meta-analysis of this outcome. All reported adverse events were non-serious and originated from the gastrointestinal tract (diarrhoea, flatulence, abdominal pain, or nausea).

Lactulose or lactitol versus antibiotics

Description of trials

Twelve trials with 698 patients (72% men) assessed lactulose or lactitol versus antibiotics.[79-90] All patients had cirrhosis and acute,[80, 83, 90] chronic,[79, 82, 86, 87, 89] acute or chronic,[81] or presumed chronic hepatic encephalopathy.[84, 85, 89] Nine trials assessed oral lactulose[79-82, 84-88] and three trials oral lactitol.[83, 89, 90] The daily mean dose of lactulose ranged from 30 g to 120 g (median 59 g) and of lactitol from 30 g to 60 g (median 60 g). The antibiotics were neomycin,[79-81] ribostamycin,[82] vancomycin,[83] or rifaximin.[84-90] The median duration of treatment was 15 days (range 5 to 90 days). One trial assessed all outcomes 15 days after end of treatment[89] and one reported mortality 28 days after end of treatment.[90] All other trials followed the patients only to the end of treatment.

Meta-analyses

Compared with antibiotics, patients on lactulose or lactitol had a significantly higher risk of no improvement of hepatic encephalopathy (RR 1.24, 95% CI 1.02 to 1.50, 10 trials; fig 3). We found no statistically significant difference in treatment response between aminoglycosides and rifaximin (P = 0.2 by test of interaction), or when trials were stratified by quality or form of hepatic encephalopathy. We found no statistically significant difference between non-absorbable disaccharides and antibiotics on mortality (RR 0.90, 95% CI 0.48 to 1.67, 5 trials) or adverse events (RR 1.62, 95% CI 0.57 to 4.58, 8 trials). All reported adverse events were non-serious and originated from the gastrointestinal tract (diarrhoea, flatulence, abdominal pain, or nausea). Trial results were homogenous.

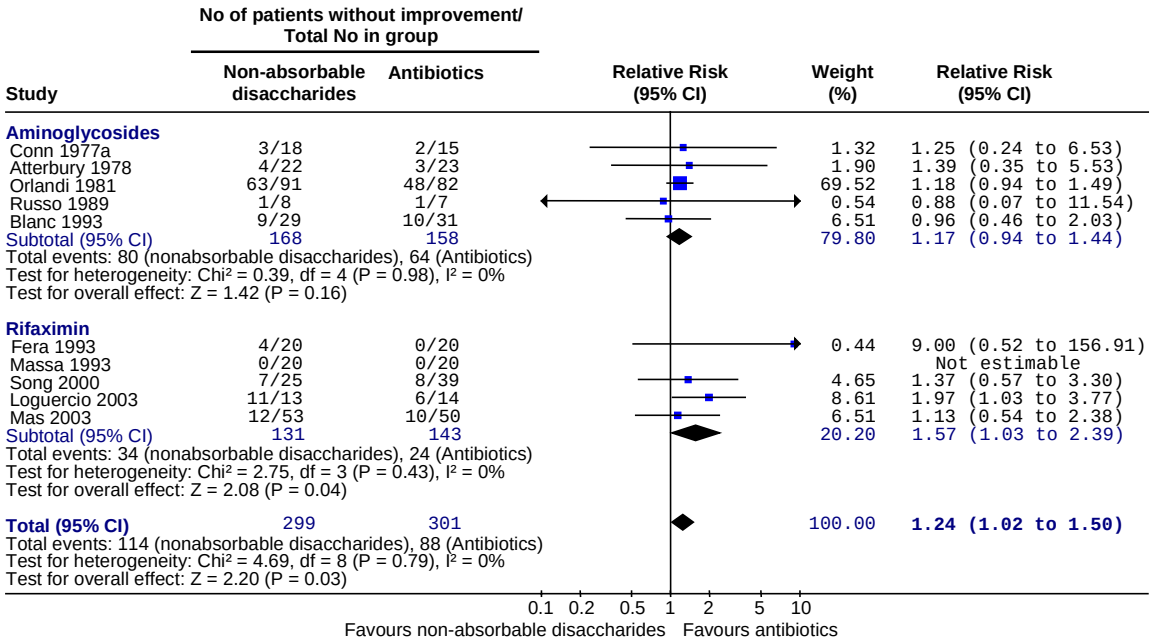

Figure 3. Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus antibiotics, stratified according to type of antibiotic

Conclusion

We did not find sufficient reliable evidence to determine whether lactulose or lactitol have a significant beneficial effect on patients with hepatic encephalopathy. The beneficial effect in low-quality trials was related to significantly worse rates of improvement in the control group. This finding suggests selection bias despite attempts

of randomisation and concurs with empirical evidence showing that low-quality trials significantly exaggerate beneficial treatment effects[61-64] We found no statistically significant effect of non-absorbable disaccharides on acute or chronic hepatic encephalopathy. Only low-quality trials in patients with minimal hepatic encephalopathy found that lactulose had a beneficial effect, as assessed by various non-validated psychometric tests. The clinical relevance of these tests is uncertain.[91]

Our analyses indicated that antibiotics are statistically superior to non-absorbable disaccharides in improving hepatic encephalopathy. However, the confidence interval is broad (1.02 to 1.50) and is close to include the point estimate of no effect.

Benzodiazepine receptor antagonists

Description of trials

Figure 4 summarises the literature search. We included 13 trials that assessed flumazenil versus placebo.[92-104] Five trials used parallel group design and eight crossover design. All trials were described as randomised, but only four reported adequate generation of the allocation sequence.[97, 99, 101, 102] Treatment allocation was adequately concealed in six trials.[94, 97-99, 101, 102] Double-blinding was reported in all trials. We classified six trials as high quality.[94, 97-99, 101, 102]

A total of 805 patients (67% men) were randomised. All patients (except five with acute liver failure) had cirrhosis and acute,[93, 103] acute or chronic,[92, 94, 95, 98, 99, 101, 102] or minimal or mild hepatic encephalopathy.[96, 97, 100, 104] Flumazenil was administered intravenously in all trials with a median dose of 2 mg (range 0.2 mg to 19.5 mg). The median duration of treatment was 10 minutes (range 1 minute to 72 hours). In one trial, patients were followed until end of hospitalisation or death,[101] and another trial followed patients one month after end of treatment.[99] All other trials followed the patients only to the end of treatment. Seven trials screened blood samples for benzodiazepines at entry.[94]

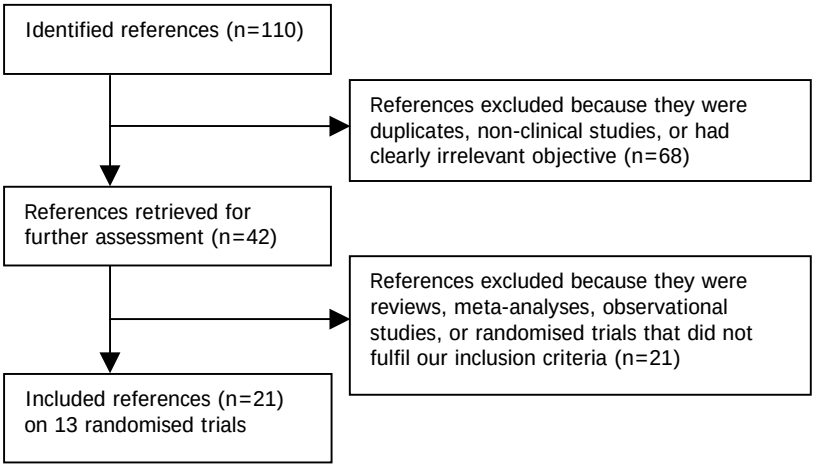

Figure 4. Selection process of eligible randomised trials on flumazenil from all identified references

Meta-analyses

Compared with placebo, flumazenil significantly reduced the risk of no improvement of hepatic encephalopathy at the end of treatment (risk difference (RD) -0.28; 95% confidence interval (CI) –0.37 to -0.20, 8 trials, fig. 5). Flumazenil had no significant effect on mortality (RD -0.01; 95% CI -0.07 to 0.05, 10 trials), or adverse events (RD 0.06; 95% CI -0.06 to 0.18, 6 trials). Trial results on improvement and mortality were homogenous. There was significant heterogeneity ($P < 0.0001$) and substantial variability ($I^2 = 83\%$) on the occurrence of adverse events across trials. This heterogeneity was due to the result of the largest trial,[102] where adverse events were not reported for any of the 527 patients receiving flumazenil. In the five other trials, 7/77 patients (9%) given flumazenil experienced adverse events (flushing, nausea, irritability, temporarily palpitations, repetitive clonic movements). There was no heterogeneity when excluding the large trial[102] ($P = 0.33$; $I^2 = 14\%$) and this meta-analysis indicated a non-significant trend towards more adverse events in the flumazenil group (RD 0.06; 95% CI -0.02 to 0.14, 4 trials). None of the trials reported that the adverse events caused dose reductions or discontinuation of therapy.

Subgroup analyses indicated that improvement of hepatic encephalopathy was not significantly associated with methodological quality, stage of hepatic encephalopathy at entry, trial design, or the presence of exogenous benzodiazepines. However, the subgroup analyses were limited by the small power to detect differences.

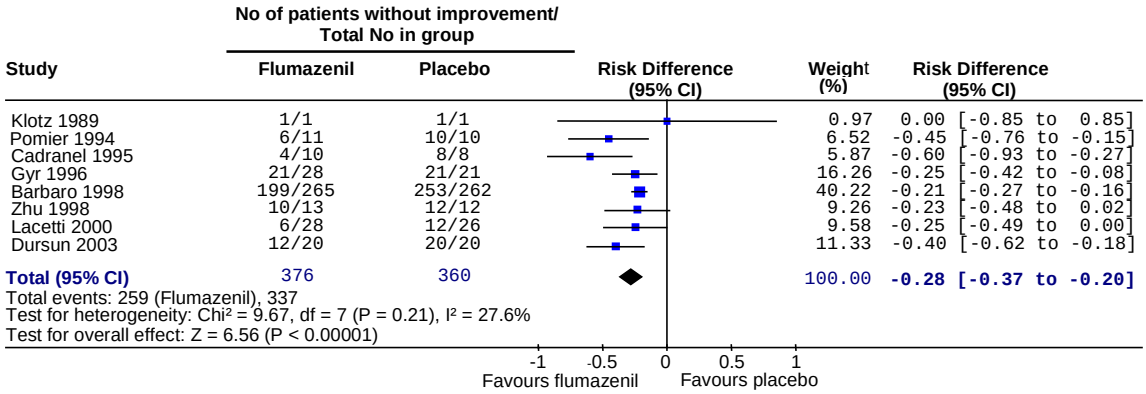

Figure 5. Number of patients without improvement of hepatic encephalopathy in trials on flumazenil versus placebo

Conclusion

Flumazenil seems to cause short-term improvement of hepatic encephalopathy in patients with cirrhosis and acute or chronic hepatic encephalopathy. However, the duration of this effect and the impact on the course of hepatic encephalopathy are uncertain. Flumazenil had no significant effect on mortality. Treatment with flumazenil may be associated with adverse events.

Trial quality was without significant effect on treatment effect. The majority of trials did not specify the type of encephalopathy or did not differentiate between patients with acute or chronic hepatic encephalopathy. Therefore, it was not possible to assess whether the treatment response differed with regard to the type of hepatic encephalopathy. The treatment response did not appear to be related to the presence of exogenous benzodiazepines.

Branched-chain amino acids

Description of trials

Figure 5 summarises the literature search. We included 11 trials[105-115] that assessed branched-chain amino acids versus placebo,[105] carbohydrates,[106] insonitrogenous control,[107-110] neomycin,[111, 112] lactulose[113, 114] and neomycin + lactulose.[115] Eight trials used a parallel group design and three a crossover design. All trials were described as randomised, but adequate generation of the allocation sequence was described in only

three.[106, 111, 112] Treatment allocation was adequately concealed in five trials.[106, 107, 109, 111, 112] Double blinding was reported in three trials.[106, 109, 111] We classified three trials as high quality.[106, 109, 111]

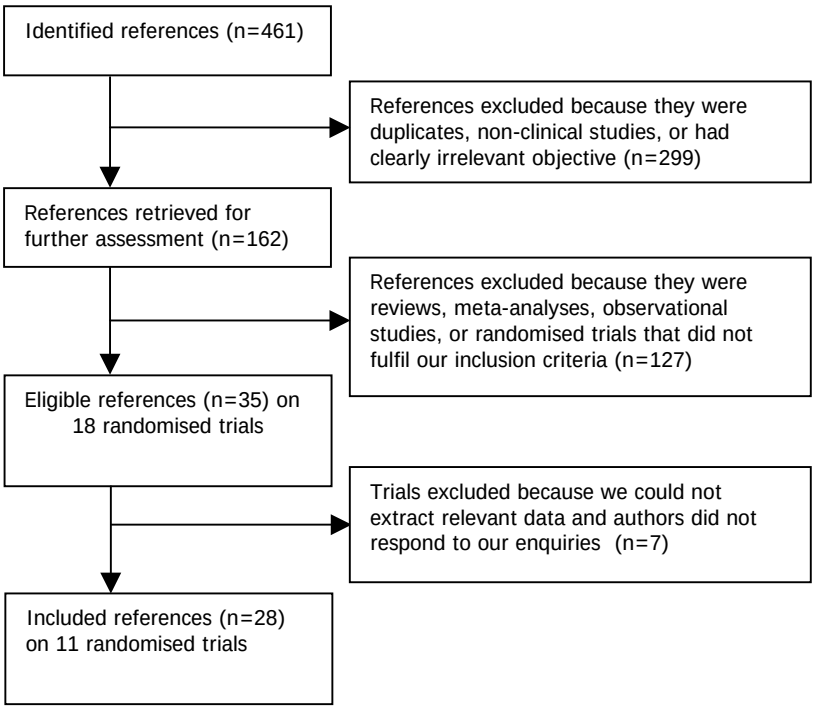

Figure 6. Selection process of eligible randomised trials on branched-chain amino acids from all identified references

A total of 556 patients (68% men) were randomised. All patients (except three with acute liver failure) had cirrhosis and acute,[106, 107, 111-115] chronic,[109, 110] or minimal hepatic encephalopathy.[105, 108] Trials of acute hepatic encephalopathy used parenteral administration of branched-chain amino acids. Trials of chronic and minimal hepatic encephalopathy used enteral administration of branched-chain amino acids. The median amount of branched-chain amino acids was 28 g/day (range 11 g to 57 g) and the median duration of treatment was seven days (range 4 to 90 days). In four trials, patients were followed after treatment (median 17 days; range 6 to 30 days).[107, 108, 111, 114]

Meta-analyses

Compared with the control regimens, branched-chain amino acids seemed to significantly reduce the risk of no improvement of hepatic encephalopathy (RR 0.75; 95% CI 0.61 to

0.92, 9 trials). This result was not robust when trials were stratified according to methodological quality. High-quality trials found no significant effect of branched-chain amino acids (RR 0.83, 95% CI 0.62 to 1.10, 3 trials), whereas low-quality trials found a significant beneficial effect (RR 0.69, 95% CI 0.50 to 0.95, 6 trials) (fig. 7). The difference in treatment response was, however, not statistically significant (P = 0.4 by test of interaction) and trial results were not significant heterogeneous, but the analyses had low power to detect differences.

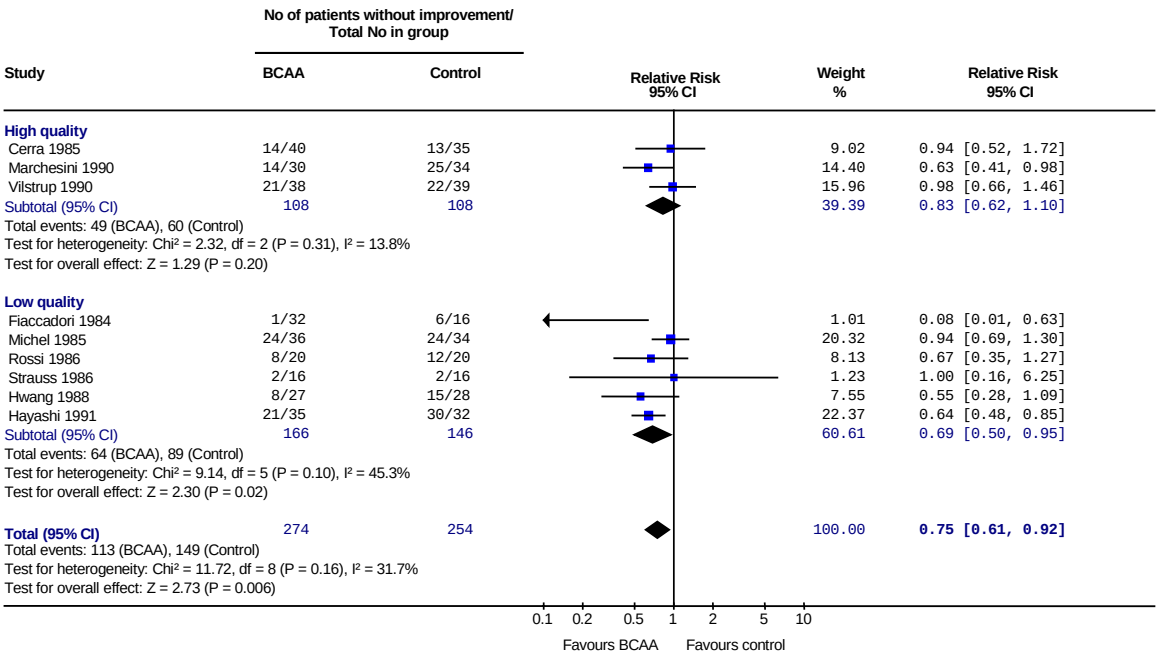

Figure 7. Number of patients without improvement of hepatic encephalopathy in trials on branched-chain amino acids versus control interventions, stratified according to quality of methods

The treatment responses of branched-chain amino acids given parenterally to patients with acute hepatic encephalopathy and branched-chain amino acids given enterally to patients with chronic hepatic encephalopathy did not differ significantly (P = 0.2 by test of interaction) (fig. 8). However, there was no significant effect of branched-chain amino acids given parenterally to patients with acute hepatic encephalopathy (RR 0.81; 95% CI 0.61 to 1.08, 7 trials). In patients with chronic hepatic encephalopathy, branched-chain amino acids given enterally significantly reduced the risk of no improvement (RR 0.64; 95% CI 0.50 to 0.81, 2 trials). The two low-quality trials on minimal hepatic encephalopathy indicated a negative effect of branched-chain amino acids in that

patients taking branched-chain amino acids on average took 25 more seconds to complete a number connection test[116] (weighted mean difference 25 seconds, 95% CI 3 to 47 seconds).

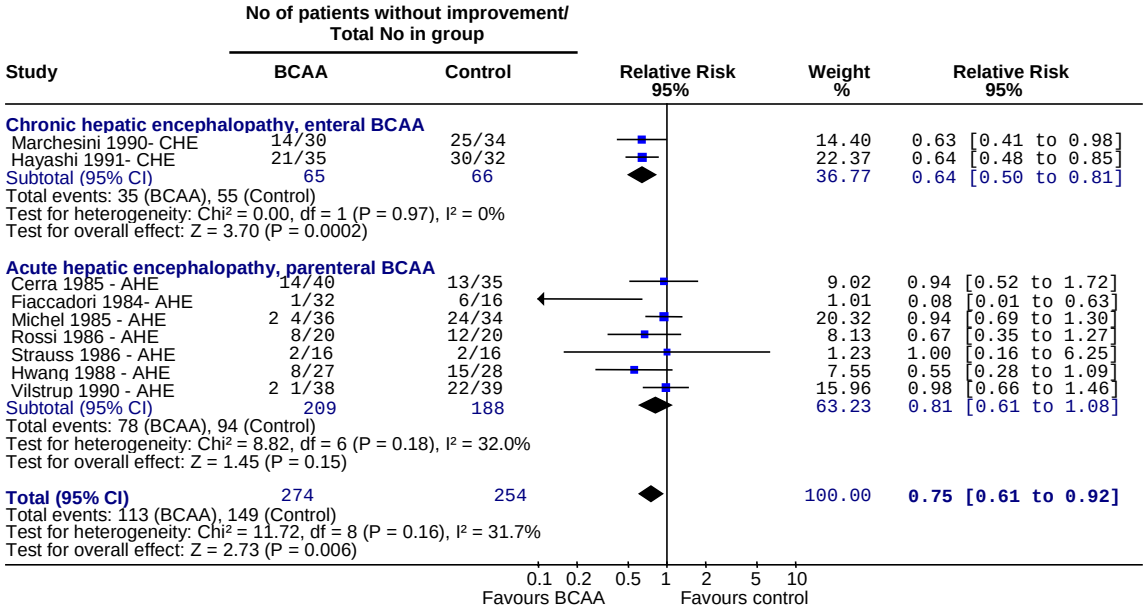

Figure 8. Number of patients without improvement of hepatic encephalopathy in trials on branched-chain amino acids, stratified according to type of hepatic encephalopathy and mode of administration

Compared with the control regimens, branched-chain amino acids had no significant effect on mortality (RR 0.85, 95% CI 0.58 to 1.25, 8 trials) or adverse events (RR 0.97; 95% CI 0.41 to 2.31, 3 trials).

Conclusion

We did not find reliable evidence that branched-chain amino acids have a significant beneficial effect on patients with hepatic encephalopathy. In our overall analysis branched-chain amino acids seemed to improve encephalopathy, but this may reflect bias because of the low methodological quality of most of the included trials.[61-64] Branched-chain amino acids had no significant beneficial effect on hepatic encephalopathy when trials with adequate generation of the allocation sequence, adequate allocation concealment, or adequate double-blinding were analysed.

We were not able to extract data from seven out of the 18 randomised trials we had located.[117-123] The excluded trials randomised a total of 81 patients. All had cirrhosis and chronic (57 patients),[117-120] minimal (24 patients),[121, 122] or either acute or chronic hepatic encephalopathy (17 patients).[123] One small trial randomising five patients with chronic encephalopathy found branched-chain amino acids were superior to lactulose.[120] All other trials found no significant effect of branched-chain amino acids compared to various control interventions. Therefore, emphasis should not be put on our subgroup analysis suggesting that branched-chain amino acids may have a more favourable effect when given enterally to patients with chronic hepatic encephalopathy than given parenterally to patients with acute hepatic encephalopathy. This difference in treatment effect is unreliable because we were unable to include several trials which failed to find a significant effect of enteral branched-chain amino acids to patients with chronic hepatic encephalopathy. Further, we were unable to determine if the difference in treatment effect was due to the type of encephalopathy, the mode of administration of branched-chain amino acids, or methodological quality of the trials. This subgroup analysis can only be considered as hypothesis generating.

Dopaminergic agonists

Description of trials

Figure 9 summarises the literature search. We included five trials that assessed bromocriptine[124, 125] or levodopa[126] versus placebo, or levodopa plus 'standard hepatic encephalopathy regime' versus 'standard hepatic encephalopathy regime'.[127, 128] Three trials used parallel group design and two crossover design. All trials were described as randomised, but adequate generation of the allocation sequence was described in only two trials.[124, 125] Treatment allocation was adequately concealed in one trial.[125] Double blinding was reported in three trials.[124-126] We classified one trial as high quality.[125]

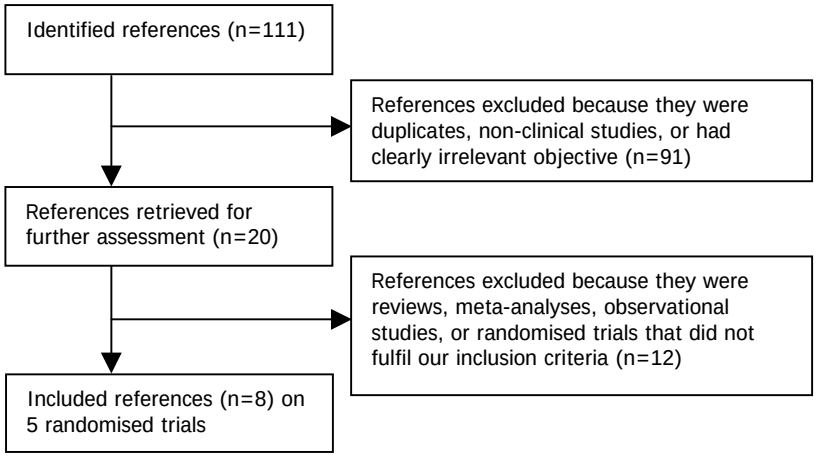

Figure 9. Selection process of eligible randomised trials on dopaminergic agonists from all identified references

A total of 144 patients (80% men) were randomised. Included patients had cirrhosis and acute hepatic encephalopathy,[126] chronic hepatic encephalopathy,[124, 125] or encephalopathy associated with acute liver failure.[127, 128] The daily mean dose of bromocriptine was 15 g and of levodopa 4 g. The median duration of treatment was 14 days (range 7 to 56 days).

Meta-analyses

Compared with placebo or no treatment, dopaminergic agonists had no significant effect on the risk of no improvement (RR 0.61; 95% CI 0.10 to 3.71, 2 trials) or mortality (RR 1.08; 95% CI 0.81 to 1.43, 4 trials) (Fig. 10). In the overall analyses, trial results were homogenous, although there was substantial variability between the study results from the two trials on levodopa for acute liver failure (I^2 = 69%).

Adverse events were reported in two trials (13 patients) and occurred in seven patients. All adverse events occurred in the experimental group and included hypomania (n = 1), hallucinations and headache (n = 1), constipation (n = 3), and nausea and vomiting (n = 2), but the occurrence was not significantly more frequent than in the placebo group (P = 0.18).

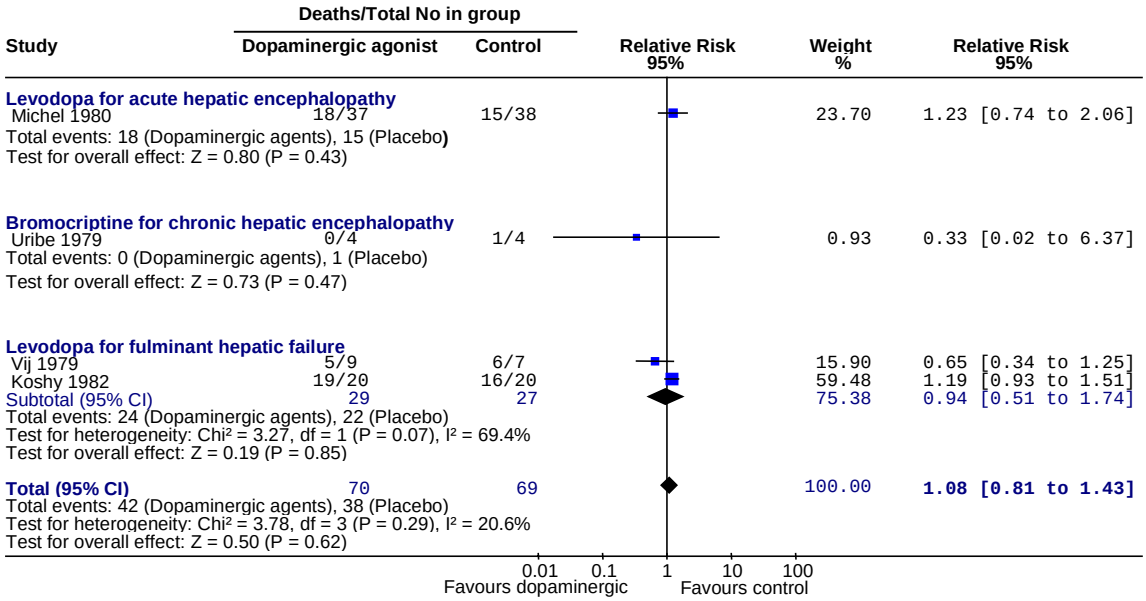

Figure 10. Number of deaths in trials on dopaminergic agonists versus control

There was no significant difference in treatment response between high- and low-quality trials (P = 0.1 by test of interaction) or between the parallel group trial assessing levodopa for acute hepatic encephalopathy and the crossover trials assessing bromocriptine for chronic hepatic encephalopathy (P = 0.3 by test of interaction). However, these analyses had very low power to detect differences.

Conclusion

We did not find evidence that dopaminergic agonists is of benefit to patients with acute or chronic hepatic encephalopathy or acute liver failure. The treatment response was not different in patients with different types of hepatic encephalopathy. However, the review is limited by the small number of trials performed within this field, the low number of patients randomised in each trial, and the low methodological quality of included trials. Accordingly, there is also insufficient evidence to exclude a potential beneficial effect.

Liver support systems

Description of trials

Figure 11 summarises the literature search. We included 12 trials that assessed artificial systems[129-138] or bioartificial systems.[139, 140] All trials used a parallel group design and were described as randomised. The allocation sequence generation was adequate in five trials[130, 133, 135, 136, 139] and the allocation concealment was adequate in nine trials.[129, 131-137, 139] Only one trial had blinded-outcome assessment and was classified as high quality.[136]

The 12 trials included 483 patients (58% men) with acute liver failure (n = 353, 73%) or acute-on-chronic liver failure (n = 130, 27%). Of the 10 trials on artificial systems, five assessed the BioLogic-DT system[131-134, 137] and two the molecular adsorbent recirculating system (MARS).[135, 136] The remaining artificial systems were whole-blood exchange,[129] charcoal hemoperfusion,[130] and plasma exchange with hemoperfusion.[138] The two trials on bioartificial systems used human liver derived tumour cells (the extracorporeal liver assist device [ELAD])[139] or porcine hepatocytes (the HepatAssist device).[140] In all trials, control groups received standard medical therapy directed against complications including electrolyte substitution, fluid substitution, antacid therapy, coagulation therapy, and N-acetylcysteine. Three trials assessed 30 days survival.[135, 136, 140] The planned duration of follow-up was not clear in the remaining trials. Based on the reported survival data, the median duration of follow-up was 28 days (range 0-33 days).

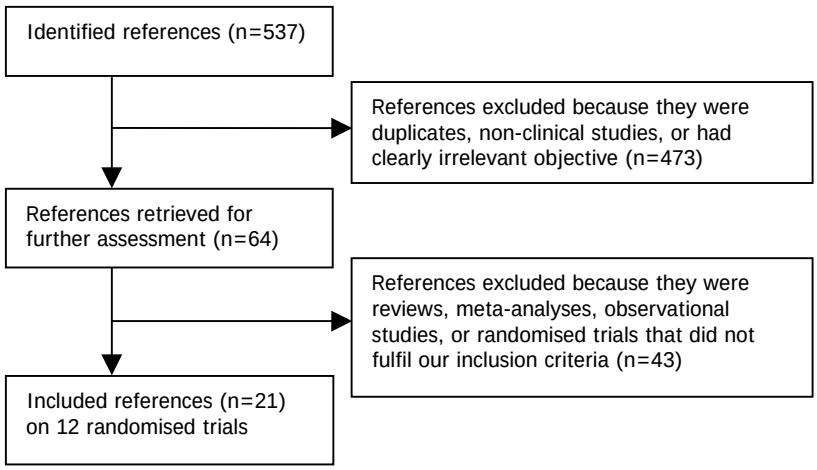

Figure 11. Selection process of eligible randomised trials on liver support systems from all identified references

Meta-analyses

Support systems had a significant beneficial effect on hepatic encephalopathy (figure 12), but no significant effect on mortality compared to standard medical therapy (RR 0.89; 95% CI 0.66 to 1.20, 12 trials). The intertrial heterogeneity was significant in the analysis on mortality (P = 0.04) and 48% of the variability between the study results could not be ascribed to sampling error (I^2 = 48%). Meta-regression indicated that the effect of support systems depended on the type of liver failure (P = 0.002). In stratified meta-analyses, support systems appeared to reduce mortality by 33% in acute-on-chronic liver failure (RR, 0.67; 95% CI, 0.51 to 0.90, 6 trials), but not in acute liver failure (RR 0.95; 95% CI 0.71 to 1.29, 8 trials). Adverse events were incompletely reported, but support systems were associated with several serious and nonserious adverse events.

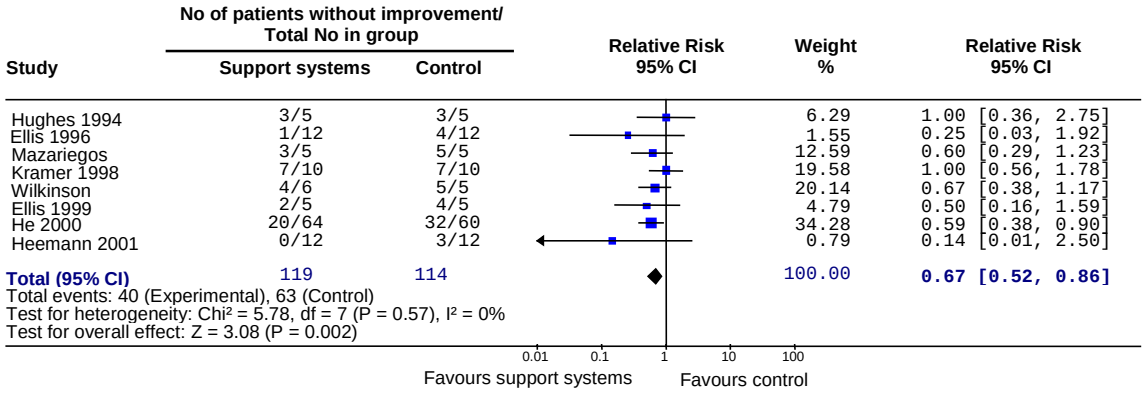

Figure 12. Number of patients without improvement of hepatic encephalopathy in trials on liver support systems versus standard medical care

Conclusion

Liver support systems seem to cause improvement of hepatic encephalopathy in patients with acute or acute-on-chronic liver failure. Overall, support systems did not appear to affect mortality, but the effect of support systems may be associated with the type of liver failure. In stratified analyses, support systems appeared to reduce mortality in acute-on-chronic liver failure, but not in acute liver failure. However, these subgroup analyses can only be considered as hypothesis generating. Support systems seemed to be associated with several adverse events, and additional randomised trials are needed before support systems can be recommended for routine use.

Discussion

The currently available reliable evidence has not shown beneficial effects of non-absorbable disaccharides, branched-chain amino acids, or dopaminergic agonists on survival or improvement of hepatic encephalopathy. However, the trials and reviews on these treatments are underpowered to draw firm conclusions; the confidence intervals include both possible beneficial and possible detrimental effects. Flumazenil had no significant effect on survival, but seems to cause short-term improvement of hepatic encephalopathy in patients with cirrhosis. However, the duration of this effect and the impact on the course of hepatic encephalopathy are uncertain. Liver support systems seem to cause improvement of hepatic encephalopathy in patients with acute or acute-on-chronic liver failure. Support systems did not appear to affect mortality, but the confidence intervals include both a possible beneficial and possible detrimental effect. Liver support systems seem to be associated with several severe adverse events. The extent to which the assessed treatments are used by physicians varies from routinely (non-absorbable disaccharides) over often (liver support systems) to seldom (dopaminergic agonist).[43]

Non-absorbable disaccharides and antibiotics

Non-absorbable disaccharides and antibiotics are considered standard treatments for hepatic encephalopathy.[43] Lactulose was introduced in the 1960s as a safer alternative to neomycin,[141] which had been standard treatment for hepatic encephalopathy since 1957.[142] Lactulose was implemented in clinical practice because two trials had found it 'equally effective' as neomycin.[79, 80] There are major pitfalls in this reasoning. Firstly, the few trials that compared lactulose against placebo did not find beneficial effect of lactulose.[70, 72] Secondly, the efficacy of neomycin on hepatic encephalopathy has never been shown. We only identified one randomised trial comparing neomycin with placebo,[143] and one comparing neomycin plus lactulose with placebo,[144] both for acute hepatic encephalopathy. Both trials found no significant beneficial effects of neomycin. Thirdly, lactulose was considered equally effective as neomycin because event rates in intervention groups were not significantly different.[79, 80] However, lack of statistical significance does not imply that treatments have equal effects.[145] Both trials[79, 80] were

small and neither reported sample size calculations based on an equivalence hypothesis or stated a margin of equivalence.[145, 146] It would require a far larger sample size than these two trials (a total of 78 patients)[79, 80] to establish with confidence that lactulose and neomycin have comparable effects.

Later on, new trials compared other antibiotics to non-absorbable disaccharides for hepatic encephalopathy. Equivalence was claimed in all the trials,[81-90, 146] but none of the trials were designed as equivalence trials, and all were underpowered to demonstrate equivalence.[145] It appears that the research was continuously building up on both insufficient evidence and insufficient methodology. Our analyses indicate that antibiotics are statistically superior to non-absorbable disaccharides in improving hepatic encephalopathy. However, the confidence interval is broad (1.02 to 1.50) and is close to include the point estimate of no effect. Considering that antibiotics have not been shown to improve encephalopathy in placebo-controlled trials,[143, 144] the effect found in the comparison with non-absorbable disaccharides may not be reliable. It may reflect a detrimental effect of non-absorbable disaccharides, a false-positive result (type 1 error), or bias. The majority of trials assessing rifaximin were industry funded, which has been shown to be associated with pro-industry results[147] and conclusions.[148-150] Considering this, the risk of multiresistance[151] and the potential risk of severe adverse events[79] lead us to conclude that there appears to be insufficient evidence to recommend antibiotics for hepatic encephalopathy. However, a systematic review on antibiotics versus placebo for hepatic encephalopathy is warranted before any firm conclusions can be made.

Non-absorbable disaccharides and antibiotics seem to have been introduced into clinical practice without appropriate documentation. This leads to at least three major problems. Firstly, patients are given treatments of uncertain efficacy. They might be beneficial; they might be unfavourable. Secondly, there is reluctance towards performing randomised trials assessing non-absorbable disaccharides or antibiotics versus placebo, because it is considered unethical. It is, however, very important to assess whether these widely used treatments are of benefit to patients with hepatic encephalopathy beyond what could be expected by chance or spontaneous remission. A recent 3-armed randomised trial compared lactitol versus rifaximin versus no treatment for the prevention of hepatic encephalopathy after transjugular intrahepatic porto-systemic

shunt (TIPS).[152] The incidence of hepatic encephalopathy was similar in the three groups.[152] Thirdly, most randomised trials on new treatments for hepatic encephalopathy use lactulose as comparator. New treatments are considered effective if improvement rates do not differ significantly from the group treated with lactulose, although trials are vastly underpowered to show equivalence. This approach is most problematic. Non-absorbable disaccharides or antibiotics should not serve as comparators in randomised trials on hepatic encephalopathy until randomised trials have shown that these treatments have significant beneficial effect on patients with hepatic encephalopathy.

Benzodiazepine receptor antagonists

We found, that flumazenil causes short-term improvement of hepatic encephalopathy in patients with cirrhosis and acute or chronic hepatic encephalopathy. Our results are in accordance with a recently published meta-analysis.[153] However, it is uncertain whether or how long time the short-term improvement (ranging from minutes to hours) lasts after end of treatment. None of the trials were designed to assess outcomes after the end of treatment. Many of the included trials reported in various terms that most patients, regardless of their response to flumazenil or placebo, regained consciousness on standard medical therapy for hepatic encephalopathy within 24 to 120 hours. The lack of focus on 'long-term' effects is possibly due to the knowledge that flumazenil has a rapid onset of action - within one to two minutes - and a short elimination half-life (0.7 to 1.3 hours).[154] As such, flumazenil has not been expected to have any 'long-term' effects. However, there are some considerations that advocate for a follow-up after the end of treatment. Firstly, having found an improvement rate of 31% at the end of treatment and considering the fluctuating nature of hepatic encephalopathy[155] it would have been appropriate to assess the length of time this beneficial effect would last after the end of treatment. Secondly, intervening and improving the state of consciousness at an early point could affect both the course of hepatic encephalopathy and diminish the occurrence of potential complications and thereby affect the number of patients surviving after the end of treatment. We did not find that flumazenil leads to a significantly higher survival rate than placebo. Future trials should assess if flumazenil leads to a sustained improvement or increased survival.

Branched-chain amino acids

Whether branched-chain amino acids are of benefit to patients with hepatic encephalopathy has been debated intensively.[156-161] Two comprehensive reviews published around the same time reached very different conclusions.[156, 157] Naylor et al meta-analysed the results from randomised trials and concluded that branched-chain amino acids increased recovery rates from acute hepatic encephalopathy but had uncertain effects on mortality.[156] Erikkson and Conn performed a narrative review scrutinising each study for its strengths and weaknesses and concluded that the majority of trials provided little evidence that branched-chain amino acids were of benefit to patients with acute, chronic, or minimal hepatic encephalopathy.[157] Although Naylor et al reached quantitative results through meta-analyses, they did not assess and incorporate the quality of the included trials in the results or interpretation of the meta-analyses. In accordance with Naylor et al, we found that branched-chain amino acids seemed to improve encephalopathy in our overall analysis. However, in accordance with Erikkson et al,[157, 159] this effect was seen only in low-quality trials. The effect in the overall analysis most likely reflects bias because of the low methodological quality.[61-64] At present, there is insufficient evidence to recommend branched-chain amino acids for hepatic encephalopathy.

Dopaminergic agonists

Guidelines state that bromocriptine may be indicated for patients with chronic encephalopathy unresponsive to other therapy.[43] Although the rationale for assessing dopaminergic agonists for hepatic encephalopathy was based on the old ‘false neurotransmitter’ hypothesis,[162] recent studies have rekindled the possible alteration of dopamine neurotransmission. New studies have shown the presence of extrapyramidal symptoms in patients with cirrhosis[163] and correlation between the symptoms and alterations in the basal ganglia, detected by magnetic resonance imaging and proton spectroscopy similar to Parkinson's disease.[164] We did not find any evidence that dopaminergic agonists are of benefit to patients with acute or chronic hepatic encephalopathy or acute liver failure. However, the review is limited by the small number of trials performed within this field and consequently, there is also insufficient evidence to exclude a potential beneficial effect. Dopaminergic agonists for hepatic

encephalopathy should not be used in clinical practice, but future trials may be of interest.

Liver support systems

We found that liver support systems reduced the risk of no improvement of hepatic encephalopathy in patients with acute or acute-on-chronic liver failure, but did not significantly reduce mortality. Due to the nature of support systems, adequate double blinding of patients and caregivers was impossible. Blinded outcome assessment could be performed, but it was only used in one trial.[136] Improvement of hepatic encephalopathy is a 'soft' outcome measure that may be influenced by the convictions of the assessor. Lack of blinding increases the risk of false positive conclusions about this outcome.[61-64] Further trials are necessary to determine the role of liver support systems in the management of patients with hepatic encephalopathy.[165]

Other treatments

Ornithine-aspartate is thought to improve hepatic encephalopathy by reducing the ammonia concentrations. Although the manufacture states that it is regarded as standard therapy for hepatic encephalopathy,[166] it is not registered in the EU or United States. It has apparently been assessed in 11 randomised trials,[167] of which only two have been published.[168, 169] All trials have been performed by Merz Pharmaceuticals who presented an individual patient data meta-analysis of five of the trials in 2000.[167] The results from the published trials and the meta-analysis seem promising. However, the fact that only two of 11 trials have been published and that only five of the trials were included in the meta-analysis warrant cautious interpretation. Consistent evidence shows that industry-sponsored research is associated with both publication delays and data withholding,[148] selective reporting of results and selective and multiple publication,[170] pro-industry results,[147] and pro-industry conclusions.[148-150] This has now led the American Medical Association to endorse a comprehensive registry of all initiated clinical trials.[171]

Sodium benzoate is also thought to improve hepatic encephalopathy by reducing the ammonia concentrations. The few randomised trials that exist have compared sodium

benzoate to lactulose.[172-174] All trials concluded that the new treatment was equally effective as lactulose, but all were underpowered to establish this with confidence. In view of the unknown efficacy of non-absorbable disaccharides, placebo-controlled trials are strongly needed.

Protein restriction has been considered a mainstay in the treatment of hepatic encephalopathy,[41] although there is no evidence that it has any clinical benefit.[39, 40] In fact, a recent trial found that protein restriction do not appear to have any beneficial effect for cirrhotic patients during an episode of encephalopathy.[37] Physicians continue, however, to restrict protein in patients with hepatic encephalopathy,[42] although the guidelines for nutrition in liver disease and transplantation of the European Society of Parenteral and Enteral Nutrition do not recommend protein restriction.[38]

Liver transplantation is always considered for patients with acute liver failure and is increasingly being used for patients with end-stage cirrhosis many of whom have hepatic encephalopathy.[41] A recent publication suggests that transplantation should already be considered after the first episode of acute hepatic encephalopathy in cirrhotic patients.[12] However, liver transplantation has never been the subject of a randomised trial, and there remains uncertainty about the magnitude of benefit and cost-effectiveness for specific patient groups.[175]

Limitations in research on hepatic encephalopathy

The research on the effects of treatments for hepatic encephalopathy is limited by several factors: the lack of shared definitions, inadequate quality, inappropriate design of trials, and lack of properly blinded placebo-controlled trials.

Assessments and definitions

During the preparation of the present reviews, a new classification and nomenclature for hepatic encephalopathy has been proposed.[3] According to this classification, all patients had type C encephalopathy (encephalopathy associated with cirrhosis and portal hypertension/or portalsystemic shunts) in the reviews assessing nonabsorbable disaccharides, benzodiazepine receptor antagonists, and branched-chain amino acids. In

the review on dopaminergic agonists patients had either type A (encephalopathy associated with acute liver failure) or type C encephalopathy. Finally, in the review on liver support systems, all patients had type A encephalopathy.

We found, that both the assessment of hepatic encephalopathy and the definition of 'improvement' covered a heterogeneous spectrum in the trials. Patients were assessed by a Glasgow coma scale, a portal-systemic encephalopathy index, a variety of psychometric tests, electroencephalograms, or clinical gradings according to Adam-Foley, Conn and Lieberthal, Benhamou, or Sherlock. The majority of trials used several different methods to assess whether patients improved. Improvement assessed by one method was often not accompanied with improvement assessed by another method. This heterogeneity in definitions of improvement reflects a general problem within the field of hepatic encephalopathy: the clinical conditions that are summarised under the term 'hepatic encephalopathy' are highly heterogeneous. Accordingly, the methods used to quantitate treatment effects and treatment outcomes are highly variable. In addition, researchers assessed different surrogate outcomes depending on their hypothesis of the underlying pathogenesis, e.g., ammonia or ratio of branched-chain amino acids and aromatic amino acids, although these correlate poorly with the severity of hepatic encephalopathy.[24, 176] In general, the scales and items used for assessing hepatic encephalopathy are arbitrary and not tested for reliability or validity. There is a substantial need for clear definitions and diagnostic criteria of hepatic encephalopathy as well as a reassessment and validation of the various scales and items using sound methodological approaches.[177] A step in this direction has been the recent consensus statement regarding hepatic encephalopathy on new terminology, definition, and diagnostic criteria.[3]

Methodological quality

Most of the trials included in our reviews were of low methodological quality. We found that low-quality trials reported larger beneficial treatment effects than high-quality trials. This had particular impact on the reviews on non-absorbable disaccharides and branched-chain amino acids, where the inclusion of low-quality trials indicated that the treatments were of benefit to patients. A meta-analysis[178] of six empirical studies of bias[61-64, 179, 180] indicate that low-quality trials significantly overestimate the benefits of

treatments by about 20%, although the impact of bias seems to vary considerably across interventions and disease areas.[178, 180] Therefore, treatment recommendations should be based on meta-analyses of high-quality trials. However, even these may be biased and tend to overestimate the benefit of the treatments due to publication bias[181, 182] and selective reporting bias.[183]

Design

Hepatic encephalopathy has a spontaneously fluctuating nature.[28] Patients' underlying condition and ability to respond to treatment might be unstable from the first to the second treatment period of crossover trials. Accordingly, the crossover design does not seem appropriate when assessing interventions for hepatic encephalopathy. However, this design is widely used in the field. In one of our reviews,[56] two-thirds of trials were crossover trials. Ideally, data from crossover trials should be analysed taking the pairing into consideration.[184] Due to the spontaneously fluctuating nature of hepatic encephalopathy, we planned a priori to include only data from the first treatment period. This seems appropriate considering that in several trials patients with clinical improvement during the first study period were not crossed over,[94, 98, 102, 111] and only few trials tested for the possibility of a carry-over or a period effect. [95, 96, 105, 108] A subgroup analysis in the review on flumazenil,[56] showed that the treatment effect was not associated with the design of the trials. Data from parallel trials were comparable with data from the first treatment period and the unpaired data from both treatment periods in crossover trials.

Placebo-controlled trials

There is a substantial need of properly placebo-controlled trials within the field of hepatic encephalopathy. The few well-conducted, placebo-controlled trials on ornithine aspartate to patients with minimal or chronic hepatic encephalopathy[168, 169] and lactulose plus neomycin[144] in acute hepatic encephalopathy found improvement rates in the placebo group ranging from 40% to 70%. It is important to compare potential treatment effects with this effect, which represents a high rate of spontaneous improvement and successful treatment of precipitating factors.

Strengths and limitations of the systematic reviews

Despite the major limitations within the clinical intervention research on hepatic encephalopathy, it is important to perform a systematic, critical appraisal of the available data. Systematic reviews have several strengths: they allow a more objective appraisal of the evidence than traditional narrative reviews, provide a more precise estimate of a treatment effect, may explain heterogeneity between the results of individual studies, and may highlight weaknesses within the research field and generate important research questions to be addressed in future studies.[185] The strengths of Cochrane Reviews are, in addition, that they are made available electronically (both on CD-ROM and the Internet) and regularly updated. The limitations of systematic reviews are primarily related to four issues: the combination of trials, the observational nature of systematic reviews, the location and selection of trials, and the validity and reporting of the included randomised trials.

Combining trials

Combining trials that were conducted in different settings and involved different types of hepatic encephalopathy may increase the generalisability and usefulness of meta-analyses,[186] although it may seem counterintuitive. However, the division of hepatic encephalopathy into different categories is arbitrary and associated with major discrepancies and controversies among specialists,[3] and several trials did not specify or differentiate between the type of hepatic encephalopathy.[56]

The results of a trial on one type of hepatic encephalopathy are likely to be extrapolated beyond that type. Aggregating all trials enabled us to assess the consistency and robustness of the treatment effects and to explore whether they differed with regard to the type of hepatic encephalopathy. In all reviews, too few patients had been randomised to reliably conclude or exclude this, but the review on liver support systems raised the hypothesis that the effect of support systems may be associated with the type of liver failure.

Observational study

As other observational studies, systematic reviews have a considerable risk of bias and confounding.[187] In order to minimise this and to enhance transparency, a systematic

review should be based on a prespecified, peer-reviewed protocol. This contains a clearly formulated question and descriptions of explicit methods in the identification, selection, and evaluation of included trials.

Selection of trials

Bias can also occur in the location and selection of trials. A comprehensive search is important not only for ensuring that as many studies as possible are identified but also to minimise selection bias for those that are found.[52] Studies that find a statistically significant effect of treatment are more likely to be published,[181] to produce multiple publications,[188, 189] and to have a significantly shorter time to publication[182] than other trials. Unpublished trials show less beneficial effects by about 9% than published trials.[190] Systematic reviews are susceptible to such publication bias, which can lead to false positive conclusions.

Validity of trials

The validity of systematic reviews depends on the quality of the included trials. Inadequate quality of trials may distort the results of systematic reviews. Empirical evidence has shown that low-quality trials significantly overestimate the benefits of treatments by about 20%.[61-64, 178-180]

The validity of systematic reviews is also threatened by selective reporting bias. Recent research has shown that the reporting of outcomes in randomised trials are frequently inadequate and biased to favour statistical significant outcomes.[183]

This overview comprises systematic reviews, which were all based on prespecified, peer-reviewed, and published protocols. In all reviews, we performed comprehensive searches of several databases and contacted authors and pharmaceutical companies. We appraised the quality of all included trials and emphasised the meta-analyses of high-quality trials in our conclusions. Nevertheless, our systematic reviews may still be prone to both reporting and publication bias. Therefore, the results of this overview may well tend to overestimate the possible benefit of the treatments for hepatic encephalopathy.

Implications for research

A number of systematic reviews on interventions for hepatic encephalopathy are warranted, eg, antibiotics versus placebo. Large, randomised double-blinded trials using sound research design and methodology[191] are strongly needed. All trials should use a parallel group design, due to the spontaneously fluctuating nature of hepatic encephalopathy. Considering the widespread use of both non-absorbable disaccharides and antibiotics, it would be relevant to determine whether these treatments are of any benefit to patients with hepatic encephalopathy. Trials should focus on patient-relevant outcomes like clinical improvement, recovery, mortality, and adverse events. Future trials should report their data according to the recommendations of the CONSORT Statement (www.consort-statement.org).[191] All trials should at their start be registered in a public database and all trial results should be made publicly available.

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Paper 1

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Papers

Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials

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Abstract

Objective To assess the effects of non-absorbable disaccharides (lactulose and lactitol) in patients with hepatic encephalopathy.
Data sources Cochrane Hepato-Biliary Group controlled trials register, Cochrane Library, Medline, and Embase until March 2003; reference lists of relevant articles; authors and pharmaceutical companies.
Review methods Randomised trials that compared non-absorbable disaccharides with placebo, no intervention, or antibiotics for hepatic encephalopathy were included. The primary outcome measures were no improvement of hepatic encephalopathy and all cause mortality.
Results 22 trials were included. Compared with placebo or no intervention, non-absorbable disaccharides seemed to reduce the risk of no improvement in patients with hepatic encephalopathy (relative risk 0.62, 95% confidence interval 0.46 to 0.84, six trials). However, high quality trials found no significant effect (0.92, 0.42 to 2.04, two trials). Compared with placebo or no intervention, non-absorbable disaccharides had no significant effect on mortality (0.41, 0.02 to 8.68, four trials). Non-absorbable disaccharides were inferior to antibiotics in reducing the risk of no improvement (1.24, 1.02 to 1.50, 10 trials) and lowering blood ammonia concentration (weighted mean difference 2.35 µmol/l, 0.06 µmol/l to 13.45 µmol/l, 10 trials). There was no significant difference in mortality (0.90, 0.48 to 1.67, five trials).
Conclusions There is insufficient evidence to support or refute the use of non-absorbable disaccharides for hepatic encephalopathy. Antibiotics were superior to non-absorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference is clinically important. Non-absorbable disaccharides should not serve as comparator in randomised trials on hepatic encephalopathy.

Introduction

Hepatic encephalopathy is a complex neuropsychiatric syndrome, which may complicate acute or chronic liver failure.[1] It is characterised by changes in mental state including a wide range of neuropsychiatric symptoms ranging from minor signs of altered brain function to deep coma.[2]

Treatment of hepatic encephalopathy aims at reducing the production and absorption of ammonia, which is involved in the pathogenesis.[3 4] As colonic bacteria are the primary source of ammonia, treatment initially consisted of poorly absorbed antibiotics, especially neomycin.[5 6] This treatment was implemented without appropriate scientific documentation. Lactulose was introduced as a safer alternative.[3] On the basis of two small trials,[5 6] lactulose was considered to be as effective as neomycin. Subsequent trials and meta-analyses concluded that lactitol and lactulose were equally effective.[7–10] Since the 1980s, non-absorbable disaccharides (lactulose and lactitol) have been considered as the standard treatment for hepatic encephalopathy.[11 12] Recent guidelines state that lactulose is the first line pharmacological treatment for hepatic encephalopathy.[12] Antibiotics can be considered a therapeutic alternative to non-absorbable disaccharides in acute hepatic encephalopathy but in chronic encephalopathy should be reserved for patients who respond poorly to non-absorbable disaccharides.[12]

We performed a systematic review to assess the beneficial and harmful effects of non-absorbable disaccharides for hepatic encephalopathy and to compare them with antibiotics.

Methods

The review was performed according to a published protocol[13] and reported according to the QUOROM statement.[14]

Searching

We searched the Cochrane Hepato-Biliary Group controlled trials register, the Cochrane Library, Medline, and Embase up to March 2003. Included terms were "hepatic encephalopathy or cirrhosis", and "lactulose, lactitol, or disaccharide", and "random* or clinical".[13] We screened bibliographies of relevant articles and conference proceedings and wrote to experts and pharmaceutical companies.

Selection—We included all randomised trials that compared non-absorbable disaccharides (lactulose and lactitol) with placebo, no treatment, or antibiotics for hepatic encephalopathy. Inclusion was regardless of publication status, language, or blinding. Included patients had acute, chronic, or minimal hepatic encephalopathy.

Validity assessment—Two reviewers independently assessed trial quality[15 16] by examining three components: generation of allocation sequence (classified as adequate if based on computer generated random numbers, tables of random numbers, or similar), concealment of allocation (classified as adequate if based on central randomisation, sealed envelopes, or similar), and blinding (classified as adequate if the trial was described as double blind or had blinded outcome assessment).[13] We classified trials with adequate concealment of allocation and adequate blinding as high quality.

Data abstraction—Two reviewers (BA-N and LLG) independently extracted data from each trial. Our primary outcome measures were the numbers of patients without improvement of hepatic encephalopathy and all cause mortality. Improvement was defined as partial or complete resolution of clinical or

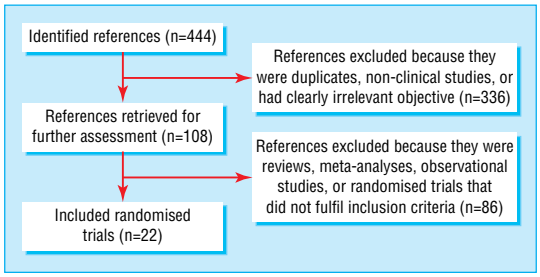

Fig 1 Selection process of eligible randomised trials from all identified references

subclinical symptoms of hepatic encephalopathy. Secondary outcome measures were adverse events, number connection test result, and blood ammonia concentration. In the number connection test, participants are instructed to connect numbers printed on a page consecutively from 1 to 25 as quickly as possible. The test score is the time the patient needs to perform the test, including the time needed to correct any errors. A low score represents a good performance. All outcomes were assessed at the end of treatment and maximum follow up.

Trial characteristics—We extracted the type and cause of the underlying liver disease, type of hepatic encephalopathy (acute, chronic, or minimal); mean age; proportion of men; number of patients randomised to each intervention arm; type, dose, and duration of treatment; mode of administration; trial quality[15 16]; trial design (parallel or crossover); duration of follow up; and number of dropouts. We sought data on all patients, irrespective of compliance or follow up. Primary investigators were contacted if data were missing.

Quantitative data synthesis—All data were analysed on the basis of intention to treat, including all randomised patients irrespective of compliance or follow up. If patients had missing outcome data, we carried forward the last reported observed response.[17] Data from the first period of crossover trials were included. Binary outcomes were expressed as relative risks with 95% confidence intervals. Continuous outcomes were expressed as weighted mean difference with 95% confidence intervals. We used a random effects model[18] because we anticipated clinical variability between trials. Statistical heterogeneity was explored by the χ^2 test with significance set at $P<0.1$. Potential sources of heterogeneity were explored through subgroup analyses with regard to the quality of methods and type of hepatic encephalopathy. We used the test of interaction[19] to compare the difference between the estimates of subgroup analyses. Analyses were performed in Review Manager version 4.2.2. for Windows and SPSS version 11.0 for Windows.

Results

Figure 1 summarises the literature search. We included 22 trials that assessed lactulose or lactitol versus placebo, no treatment, or antibiotics.[5 6 20–39] Two trials were published as abstracts.[32 37] The remaining were published as full articles. Eighteen trials used a parallel group design and four a crossover design. All trials were described as randomised, but adequate generation of the allocation sequence was described in only four.[22 30 31 39] Treatment allocation was adequately concealed in 10 trials,[5 6 20–23 26 30 36 39] double blinding was reported in 15 trials,[5 6 20–25 27 32–34 36 38 39] and one trial had blinded outcome assessment.[30] We classified nine trials as high quality.[5 6 20–23 30 36 39]

Lactulose or lactitol *v* placebo or no intervention

Ten trials with 280 patients (75% men) assessed lactulose or lactitol versus placebo or no intervention (table 1).[20–29] All patients had cirrhosis and acute,[25] chronic,[20 22–24] acute or chronic,[21] or minimal hepatic encephalopathy.[26–29] Eight trials assessed oral lactulose,[20–24 26 28 29] one assessed oral lactitol,[27] and one assessed lactitol enemas.[25] The daily mean doses of lactulose ranged from 30 g to 84 g (median 50 g). In six trials the dose was adjusted to obtain two to three semisoft stools per day. The median duration of treatment was 15 days (range 5 to 360 days). None of the trials followed up patients after the end of treatment.

Trial results were homogeneous. Compared with placebo or no intervention, lactulose and lactitol seemed to reduce the risk of no improvement of hepatic encephalopathy (relative risk 0.62, 95% confidence interval 0.46 to 0.84, six trials; fig 2). This result was not robust when trials were stratified by quality. High quality trials found no significant effect of lactulose or lactitol on the risk of no improvement (0.92, 0.42 to 2.04, two trials; fig 2), whereas low quality trials found a significant beneficial effect of lactulose or lactitol (0.57, 0.40 to 0.83, four trials; fig 2). Although this difference in treatment response was not significant ($P=0.3$ by test of interaction), it is noteworthy that the event rate in the control groups was significantly associated with quality of methods (high quality trials 38%, low quality trials 78%; $P=0.0005$ with χ^2 test). The event rate in the experimental group was not significantly different in trials with high (35%) and low (43%) quality ($P=0.5$ with χ^2 test). The treatment responses in acute, chronic, and minimal hepatic encephalopathy did not differ significantly. However, there was no significant effect of lactulose or lactitol on

Table 1 Randomised trials of non-absorbable disaccharides versus placebo or no intervention in treatment of patients with hepatic encephalopathy

	Study design	Quality*	No of patients randomised	Type of hepatic encephalopathy	Experimental/control intervention	No of patients without improvement/total†		No of dropouts/total	
						Experimental	Control	Experimental	Control
Elkington 1969[20]	Crossover	High	7	Chronic	Lactulose/sorbitol	‡		Not described	
Simmons 1970[21]	Parallel	High	26	Acute + chronic	Lactulose/glucose	4/14	5/12	3/14	2/12
Rodgers 1973[22]	Crossover	High	6	Chronic	Lactulose/sorbitol	‡		3	
Germain 1973[23]	Parallel	High	18	Chronic	Lactulose/saccharose	4/9	3/9	None	
Corazza 1982[24]	Parallel	Low	32	Chronic	Lactulose/placebo	§		Unknown	
Uribe 1987[25]	Parallel	Low	15	Acute	Lactitol enemas/tap water enemas	0/10	4/5	Unknown	
Watanabe 1997[26]	Parallel	Low	36	Minimal	Lactulose/no treatment	12/22	11/14	2/22	1/14
Shi 1997[27]	Parallel	Low	31	Minimal	Lactitol/glucose	§		Unknown	
Li 1999[28]	Parallel	Low	86	Minimal	Lactulose/no treatment	22/48	27/38	Unknown	
Dhiman 2000[29]	Parallel	Low	26	Minimal	Lactulose/no treatment	6/14	12/12	4/14	4/12

*Classified with adequate allocation concealment and adequate blinding as high quality.
†Improvement defined as partial or complete resolution of clinical or subclinical symptoms of hepatic encephalopathy.
‡Lactulose and sorbitol reported to be equally effective, but numerical data not available.
§Lactulose/lactitol reported to be superior to placebo, but numerical data not available.

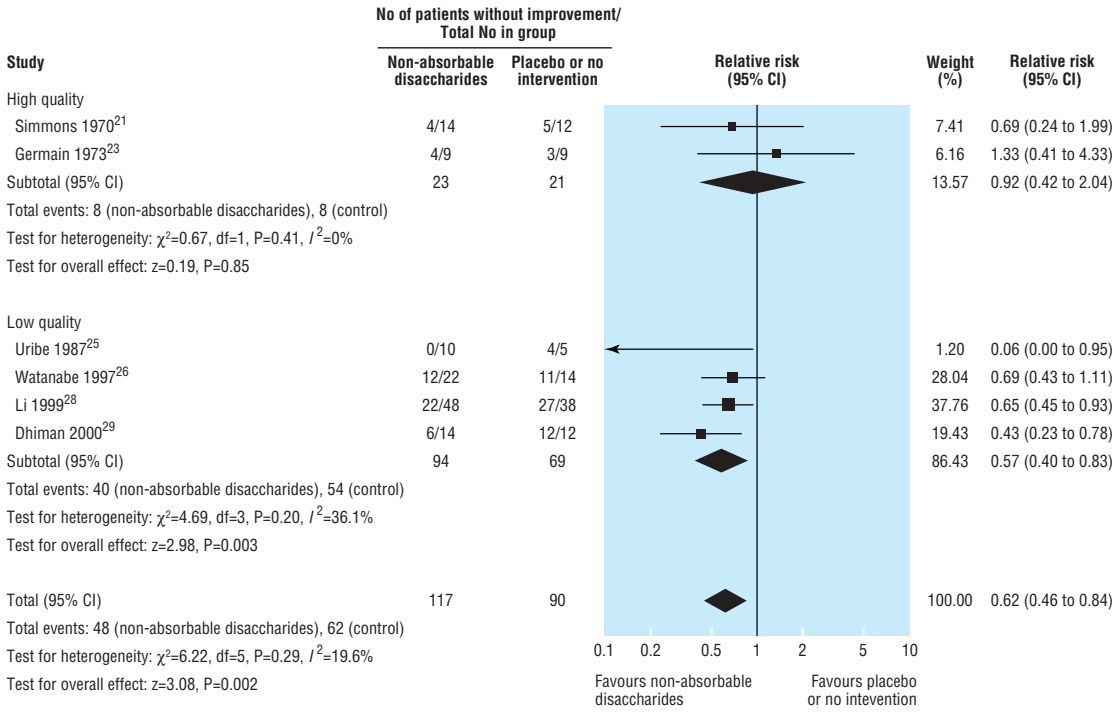

Fig 2 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus placebo or no intervention, stratified according to quality of methods

acute (0.27, 0.02 to 3.28, two trials) or chronic hepatic encephalopathy (1.33, 0.41 to 4.33, one trial). Trials in patients with minimal hepatic encephalopathy found that lactulose or lactitol significantly reduced the risk of no improvement assessed by various psychometric tests (0.61, 0.47 to 0.79, three trials). These trials were all of low methodological quality.

Compared with placebo or no intervention, lactulose and lactitol had no significant effect on mortality (0.41, 0.02 to 8.68, four trials) or the number connection test result (weighted mean difference −9.0 seconds, −20.1 to 2.1, one trial) but tended to lower blood ammonia (−8.16 µmol/l, −16.44 µmol/l to 0.18 µmol/l, four trials). Data on adverse events were incompletely reported. Most trials mentioned adverse events associated only with non-absorbable disaccharides. We were therefore unable to perform a reliable meta-analysis of this outcome. None of the reported adverse events were serious, and all originated from the gastrointestinal tract (diarrhoea, flatulence, abdominal pain, or nausea).

Lactulose or lactitol versus antibiotics

Twelve trials with 698 patients (72% men) assessed lactulose or lactitol versus antibiotics (table 2).[5 6 30–39] All patients had cirrhosis and acute,[6 32 39] chronic,[5 31 35 36 38] acute or chronic,[30] or presumed chronic hepatic encephalopathy.[33 34 37] Nine trials assessed oral lactulose,[5 6 30 31 33–37] and three trials assessed oral lactitol.[32 38 39] The daily mean dose of lactulose ranged from 30 g to 120 g (median 59 g) and of lactitol from 30 g to 60 g (median 60 g). The antibiotics were neomycin,[5 6 30] ribostamycin,[31] vancomycin,[32] or rifaximin.[33–39] The median duration of treatment was 15 days (range 5-90 days). One trial assessed all outcomes 15 days after the end of treatment,[38] and one reported mortality 28 days after the end of treatment.[39] All other trials followed the patients only to the end of treatment.

Trial results were homogeneous. Compared with antibiotics, patients taking lactulose or lactitol had a significantly higher risk of no improvement of hepatic encephalopathy (1.24, 1.02 to 1.50, 10 trials; fig 3). We found no significant difference in response to treatment between aminoglycosides and rifaximin (P = 0.2 by test of interaction) or when trials were stratified by quality or type of hepatic encephalopathy. We found no significantly different effect on mortality between non-absorbable disaccharides and antibiotics (0.90, 0.48 to 1.67, five trials) or on adverse events (1.62, 0.57 to 4.58, eight trials). None of the reported adverse events were serious, and all originated from the gastrointestinal tract (diarrhoea, flatulence, abdominal pain, or nausea). Compared with antibiotics, patients on lactulose or lactitol took on average six more seconds to complete the number connection test (weighted mean difference 6.4 seconds, 1.4 seconds to 11.3 seconds, six trials) and had higher blood ammonia concentrations (2.35 µmol/l, 0.06 µmol/l to 4.64 µmol/l, 10 trials).

Discussion

We did not find sufficient evidence to determine whether lactulose or lactitol have a significant beneficial effect on patients with hepatic encephalopathy. In our overall analysis non-absorbable disaccharides seemed to improve encephalopathy, but this effect was seen in only low quality trials.

The beneficial effect in low quality trials was related to significantly worse rates of improvement in the control group. This finding concurs with empirical evidence showing that low quality trials exaggerate the beneficial effects of treatment.[15 16 40] Accordingly, the overall result may reflect bias because of the low methodological quality of most of the included trials. Our results may also be inflated by publication bias.

We found no significant effect of non-absorbable disaccharides on acute or chronic hepatic encephalopathy. Only low quality trials in patients with minimal hepatic encephalopathy found that lactulose had a beneficial effect, as assessed by various

Table 2 Randomised trials on non-absorbable disaccharides versus antibiotics in treatment of patients with hepatic encephalopathy

	Study design	Quality*	No of patients randomised	Type of hepatic encephalopathy	Experimental/control intervention	No of patients without improvement/total†		No of dropouts/total	
						Experimental	Antibiotics	Experimental	Antibiotics
Conn 1977[5]	Crossover	High	33	Chronic	Lactulose + placebo/neomycin + sorbitol	3/18	2/15	None in 1st period	
Atterbury 1978[6]	Parallel	High	47	Acute	Lactulose + placebo/neomycin + sorbitol	4/23	4/24	1/23	1/24
Orlandi 1981[30]	Parallel	High	190	Acute + chronic	Lactulose/neomycin + magnesium sulfate	63/91	48/82		17§
Russo 1989[31]	Crossover	Low	15	Chronic	Lactulose/ribostamycin	1/8	2/7	Unknown	
Blanc 1993[32]	Parallel	Low	60	Acute	Lactitol/vancomycin	9/29	10/31	2/29	2/31
Bucci 1993[33]	Parallel	Low	58	Unknown	Lactulose + placebo/rifaximin + sorbitol	‡		Unknown	
Fera 1993[34]	Parallel	Low	40	Unknown	Lactulose + placebo/rifaximin + placebo	4/20	0/20	Unknown	
Festi 1993[35]	Parallel	Low	21	Chronic	Lactulose/rifaximin	‡		Unknown	
Massa 1993[36]	Parallel	High	40	Chronic	Lactulose + placebo/rifaximin + sorbitol	2/20	0/20	Unknown	
Song 2000[37]	Parallel	Low	64	Unknown	Lactulose/rifaximin	7/25	8/39	1/25	1/39
Loguercio 2003[38]	Parallel	Low	27	Chronic	Lactitol + placebo/rifaximin + placebo	11/13	6/14	3/13	2/14
Mas 2003[39]	Parallel	High	103	Acute	Lactitol + placebo/rifaximin + placebo	12/53	10/50	7/53	8/50

*Classified with adequate allocation concealment and adequate blinding as high quality.
†Improvement defined as partial or complete resolution of clinical or subclinical symptoms of hepatic encephalopathy.
‡Experimental and control intervention reported to be equally effective but numerical data not available.
§Exact number of dropouts in each intervention group not reported and accordingly it was not possible to perform intention to treat analysis for this trial.

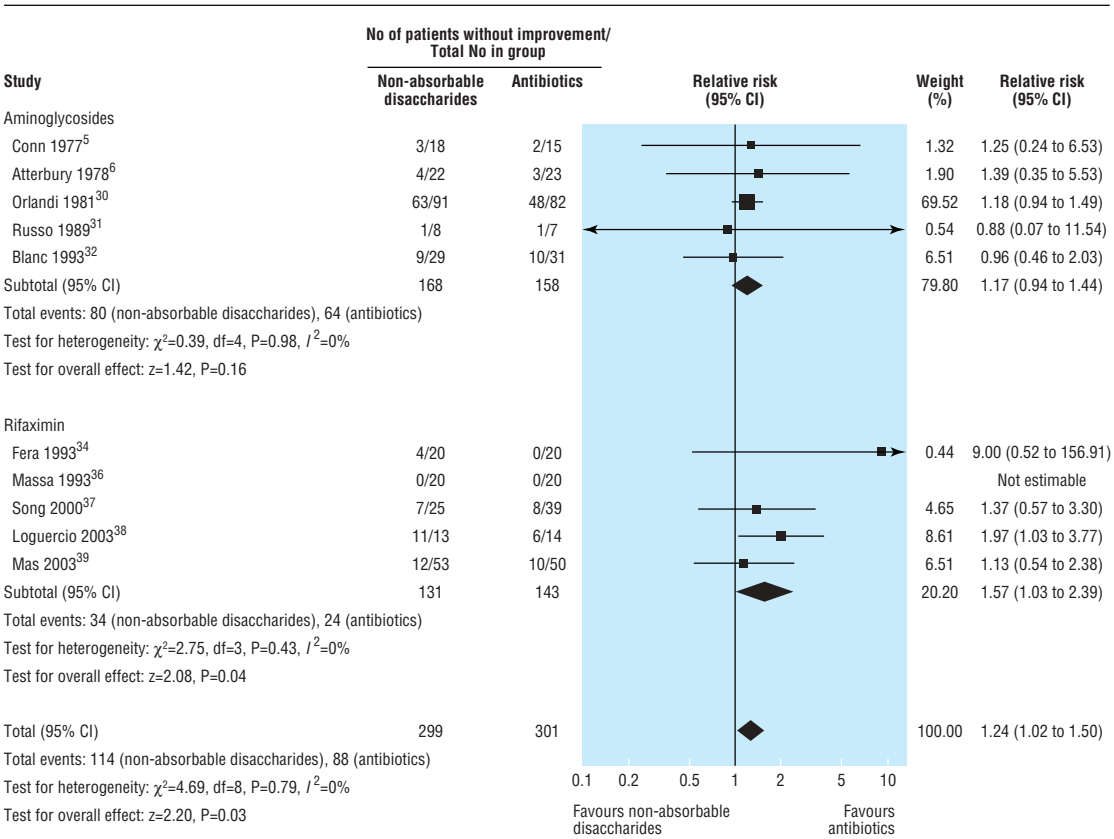

Fig 3 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus antibiotics, stratified according to type of antibiotic

non-validated psychometric tests. The clinical relevance of these tests is uncertain.[41]

Lactulose has been used as the standard treatment for hepatic encephalopathy, and its efficacy has been considered to be beyond doubt.[2 7 24 25 42] However, when it was introduced, the few trials that compared lactulose against placebo found no beneficial effect of lactulose.[21 23] It was implemented in clinical practice because two trials found it "equally effective" to neomycin,[5 6] which had been the standard treatment for hepatic encephalopathy since 1957.[43] There are two major pitfalls in this reasoning. Firstly, the efficacy of neomycin in hepatic encephalopathy has never been shown. We identified only one randomised trial that compared neomycin with placebo[44] and one that compared neomycin plus lactulose with placebo,[45] both for acute hepatic encephalopathy. Both trials found no significant beneficial effects of neomycin. Secondly, lactulose was considered as equally effective to neomycin because event rates in intervention groups were not significantly different.[5 6] However, lack of statistical significance does not imply that treatments have equal effects.[46] Both trials were small,[5 6] and neither reported sample size calculations based on an equivalence hypothesis or stated a margin of equivalence.[46 47] It would require a far larger sample size than these two trials (a total of 78 patients) to establish with confidence that lactulose and neomycin have comparable effects.

Later on, new trials compared other antibiotics to non-absorbable disaccharides for hepatic encephalopathy. None was set up as an equivalence trial. Sample size calculations with statements implying an equivalence hypothesis or a margin of equivalence were not reported in any of the trials. All were underpowered to show equivalence. Nevertheless, all trials concluded equivalence from the lack of statistical significance.[30–39] It seems that the research was continuously building up on both insufficient evidence and inadequate methods. Our analyses indicate that antibiotics are statistically superior to non-absorbable disaccharides in improving hepatic encephalopathy and lowering blood ammonia concentrations. However, it is unclear whether the effects are clinically important. Considering this, the lack of effect of antibiotics in placebo controlled trials,[44 45] the risk of multiresistance,[48] and the potential risk of severe adverse events[5] lead us to conclude that there is insufficient evidence to recommend the use of antibiotics for hepatic encephalopathy.

Mechanisms

When assessing intervention effects for hepatic encephalopathy, it is important to consider the fluctuating course as well as the impact of treating precipitating factors in acute hepatic encephalopathy. Well conducted placebo controlled trials on the use of ornithine aspartate in patients with minimal or chronic hepatic encephalopathy[49 50] and lactulose plus neomycin[45] in those with acute hepatic encephalopathy found improvement rates in the placebo group ranging from 40% to 70%. Many clinicians claim to have witnessed beneficial effects of non-absorbable disaccharides on patients with hepatic encephalopathy. This effect may represent a high rate of spontaneous improvement and successful treatment of precipitating factors.

Implications

Non-absorbable disaccharides seem to have been introduced into clinical practice without appropriate documentation. This leads to at least three major problems. Firstly, patients are given a treatment of uncertain efficacy. It might be beneficial; it might be unfavourable. Secondly, there is reluctance towards performing randomised trials to assess lactulose or lactitol versus placebo because it is considered unethical. Thirdly, most randomised trials on new treatments for hepatic encephalopathy use lactulose as comparator. New treatments are considered effective if improvement rates do not differ significantly from the group treated with lactulose, although trials are vastly underpowered to show equivalence. This approach is most problematic. Non-absorbable disaccharides should not serve as comparator in randomised trials on hepatic encephalopathy until other trials have shown that lactulose or lactitol has any beneficial effect on hepatic encephalopathy.

What is already known on this topic

Non-absorbable disaccharides are considered standard treatment for hepatic encephalopathy

Non-absorbable disaccharides serve as control treatment in most trials of new drugs for hepatic encephalopathy

What this study adds

There is insufficient evidence to determine whether non-absorbable disaccharides are of benefit to patients with hepatic encephalopathy

Antibiotics seem superior to non-absorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference is clinically important

Non-absorbable disaccharides should not be used as the comparator in randomised trials on hepatic encephalopathy

We thank the patients who took part in the reviewed trials; the researchers who provided us with additional information; Jørgen Hilden, department of biostatistics, University of Copenhagen, for statistical support; and Peter Gøtzsche, Nordic Cochrane Centre, for valuable comments on an earlier draft of this review. This review is an abbreviated version of a Cochrane systematic review. The full version will be published in the Cochrane Library 2004, Issue 2. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms, and the Cochrane Library should be consulted for the most recent version of the review.

Contributors: BA-N drafted the protocol and paper, performed the literature searches, identified trials, extracted data, and performed the statistical analyses. LLG identified trials and extracted data. All reviewers contributed to the writing of the protocol and review and all have approved of the final version. BA-N is guarantor.

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Ethical approval: Not required.

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Paper 2

Benzodiazepine receptor antagonists for hepatic encephalopathy

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This is a reprint of a Cochrane review, prepared and maintained by the Cochrane Collaboration and published in *The Cochrane Library* 2004, Issue 3

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ABSTRACT

Background
Hepatic encephalopathy may be associated with accumulation of substances that bind to a receptor-complex in the brain resulting in neural inhibition. Benzodiazepine receptor antagonists may have a beneficial effect on patients with hepatic encephalopathy.

Objectives
To evaluate the beneficial and harmful effects of benzodiazepine receptor antagonists for patients with hepatic encephalopathy.

Search strategy
Eligible trials were identified through *The Cochrane Hepato-Biliary Group Controlled Trials Register*, *The Cochrane Controlled Trials Register on The Cochrane Library*, *MEDLINE* and *EMBASE* (last search: January 2004), reference lists of relevant articles, authors of trials, and pharmaceutical companies.

Selection criteria
Randomised trials comparing any benzodiazepine receptor antagonist versus placebo or no intervention for hepatic encephalopathy.

Data collection and analysis
Two reviewers independently included trials and extracted data. Binary outcomes are reported as risk difference (RD) with 95% confidence intervals (CI) based on a random effects model. Statistical heterogeneity was explored by a chi-squared test with significance set at $P < 0.1$. The inconsistency across trials was assessed by I^2. Potential sources of heterogeneity were explored through subgroup analyses.

Main results
Thirteen randomised trials with 805 patients were included. Eight trials used a crossover design. All trials were double-blind and assessed flumazenil versus placebo. Data on all outcomes could not be extracted from all trials. The included patients had a favourable prognosis (361/390 [93%] survived in the flumazenil group versus 345/376 [92%] in the placebo group). Flumazenil had a significant beneficial effect on improvement of hepatic encephalopathy at the end of treatment (RD 0.28; 95% CI 0.20 to 0.37, eight trials). Flumazenil had no significant effect on recovery (RD 0.13; 95% CI -0.09 to 0.36, two trials) or mortality RD 0.01; 95% CI -0.05 to 0.07, 10 trials). Flumazenil may be associated with adverse events, but trial results were heterogeneous.

Reviewers' conclusions
Flumazenil had a significant beneficial effect on short-term improvement of hepatic encephalopathy in patients with cirrhosis and a highly favourable prognosis. Flumazenil had no significant effect on recovery or survival. Considering the fluctuating nature of hepatic encephalopathy, future trials should use a parallel design and assess if treatment with flumazenil leads to a sustained improvement or increased recovery and survival. Until this has been demonstrated, flumazenil may be considered for patients with chronic liver disease and hepatic encephalopathy, but cannot be recommended for routine clinical use.

BACKGROUND

Hepatic encephalopathy refers to a complex neuropsychiatric syndrome, which may complicate acute or chronic hepatic failure (Gitlin 1996). It is characterised by changes in mental state including a wide range of neuropsychiatric symptoms ranging from minor not readily discernible signs of altered brain function, overt psychiatric and/or neurological symptoms to deep coma (Conn 1979). Accordingly, the methods to estimate treatment effects and treatment outcomes are highly variable (Ferenci 1997). The majority of hepatic encephalopathy occurs in patients with cirrhosis, often associated with spontaneous or iatrogenic portal-systemic shunting (Jones 1993).

Hepatic encephalopathy is generally considered a reversible metabolic encephalopathy (Gitlin 1996). Traditionally, hepatic encephalopathy has been considered to be secondary to the accumulation of toxic products, which have not been metabolised by the liver (Gitlin 1996). Various hypotheses have been suggested, e.g., alterations in the permeability of the blood-brain barrier, abnormal neurotransmitter balance, altered cerebral metabolism, and increased amounts of endogenous benzodiazepine-like compounds - the gamma-amino butyric acid (GABA)/benzodiazepine hypothesis (Jones 1984). GABA is the principal inhibitory neurotransmitter in mammals. GABA acts by binding to a receptor on a 'supramolecular complex' called the GABA/benzodiazepine complex, which also has binding sites for benzodiazepines and barbiturates. By binding to the GABA/benzodiazepine complex, benzodiazepines cause sedation through neural inhibition (Chang 1982; Schoch 1985). It has been suggested that liver failure leads to the accumulation of substances that bind to the GABA/benzodiazepine complex resulting in neural inhibition which may progress to coma (Schafer 1982; Mullen 1988; Basile 1991). Accordingly, a benzodiazepine-receptor antagonist, flumazenil (Whitwam 1995), has been assessed in the treatment of hepatic encephalopathy in the hope of reversing neuropsychiatric symptoms related to the accumulation of endogenous benzodiazepine-like substances (Pomier 1994; Amodio 1997; Barbaro 1998).

Several randomised trials have assessed the efficacy of flumazenil for hepatic encephalopathy (Amodio 1997; Pomier 1994; Barbaro 1998), but there are several methodological problems with them. First, the statistical power of most trials is weak and the conclusions are disparate. Second, several randomised trials have been designed as crossover trials using short washout periods. This impedes the evaluation of clinical outcomes after the end of treatment including the assessment of how long a potential beneficial effect would last and if a beneficial effect could affect the course of hepatic encephalopathy or survival. Furthermore, the crossover design is not suitable in situations when the condition of patients and their ability to respond to treatment is not stable over time (period effects). Third, due to the variability of hepatic encephalopathy, neither study populations nor methods to evaluate the outcomes have been standardised. A meta-analysis on six randomised trials published as an abstract in 1998 (Goulenok 1998) and a full-paper in 2002 (Goulenok 2002)compared flumazenil versus placebo for hepatic encephalopathy. The meta-analysis suggested that flumazenil may induce clinical improvement. Two of the included studies (Groeneweg 1996; Gyr 1996) refer to the same trial, and new randomised trials have been published.

OBJECTIVES

To evaluate the beneficial and harmful effects of benzodiazepine receptor antagonists in patients with hepatic encephalopathy.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included all randomised trials, irrespective of blinding, publication status, or language. Unpublished trials were included if we could get access in written form of the methodology and the data of the trial. Trials in which patients were allocated by a quasi-random method, e.g., day of birth or date of admission, were excluded.

Types of participants

Patients with hepatic encephalopathy in connection with acute or chronic liver diseases or fulminant hepatic failure were included. Patients of either gender, any age or ethnic origin were included, irrespective of the aetiology of the liver disease and the factors precipitating the hepatic encephalopathy.

Acute hepatic encephalopathy involves an abrupt onset of neuropsychiatric symptoms in patients with chronic liver disease. Acute hepatic encephalopathy may be idiopathic or precipitated by one or more causes including infections, gastrointestinal bleeding, electrolyte or acid-base disturbances, constipation, medications, hypo- or hyperglycaemia, renal dysfunction, large protein meals, alcohol withdrawal, or a superimposed acute liver disease.

Chronic hepatic encephalopathy involves persistent neuropsychiatric dysfunction in patients with chronic liver disease. The onset is usually insidious and the dysfunction may be clinically overt (i.e., chronic hepatic encephalopathy) or only demonstrable by psychometric testing (i.e., subclinical encephalopathy also known as latent or minimal hepatic encephalopathy).

Fulminant hepatic failure is a severe stage of hepatic functional deterioration in patients without underlying liver disease. The main clinical features are hepatic encephalopathy and direct symptoms of liver cell damage, mainly jaundice and coagulation disorders (Bernuau 1999).

Types of intervention

Benzodiazepine receptor antagonists in any dose or duration versus placebo or no intervention. Additional interventions were allowed if received by both intervention arms.

Types of outcome measures

(1) Recovery.
(a) Number of patients recovering from hepatic encephalopathy. Recovery was defined as a complete resolution of clinical symptoms of hepatic encephalopathy.
(b) Time to recovery, i.e., the number of minutes/hours/days with hepatic encephalopathy from the time of randomisation to recovery.

(2) Improvement.
(a) Number of patients with improvement of hepatic encephalopathy using the definitions of the individual trials, e.g., clinical grading, electrophysiological testing, psychometrical testing, or summary grading including the Portal-systemic Encephalopathy Index (Conn 1977; Blei 1999).
(b) Time to improvement, i.e., the number of minutes/hours/days from the time of randomisation to improvement.

(3) Survival.
Number of patients surviving at the maximum follow-up of the individual trial.

(4) Quality of life.

(5) Number and types of adverse events. Adverse events were graded as serious and non-serious according to the International Conference on Harmonisation Guidelines (ICH-GCP 1997).

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

The Cochrane Hepato-Biliary Group Controlled Trials Register, *The Cochrane Central Register of Controlled Trials (CENTRAL)*, *MEDLINE on SilverPlatter*, and *EMBASE* were searched January 12, 2004 using the search strategies specified in Table 01.

The reference lists of relevant articles were scanned for additional trials. The principal authors of the identified clinical trials and pharmaceutical companies involved in the production of benzodiazepine receptor antagonists were inquired about additional trials they might know of.

METHODS OF THE REVIEW

Selection of trials

Decisions on which trials to include were taken independently by two contributors (BAN and LLG) who were unblinded with regard to the names of the authors, investigators, institution, source, and results. Disagreements were resolved by discussion. Excluded trials were listed with the reason for exclusion.

Methodological quality

The methodological quality of each trial was evaluated independently by BAN and LLG. The methodological quality was assessed by the following components (Jadad 1996; Schulz 1995; Moher 1998; Kjaergard 2001).

Generation of the allocation sequence
Adequate: by table of random numbers, computer generated random numbers, coin tossing, shuffling, or similar.
Unclear: if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
Inadequate: if a system involving dates, names, or admittance numbers were used for the allocation of patients. Such trials were excluded from the review.

Allocation concealment
Adequate: if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
Unclear: if the trial was described as randomised, but the method used to conceal the allocation was not described.
Inadequate: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding
Adequate: if the trial was described as double-blind and the method of blinding involved identical placebo or active drugs.
Unclear: if the trial was described as double-blind, but the method of blinding was not described.
Not performed: if the trial was not double-blind or the method of blinding was inappropriate.

Follow-up
Adequate: if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
Unclear: if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
Inadequate: if the number or reasons for dropouts and withdrawals were not described.

We classified trials with adequate allocation concealment and adequate double-blinding as high quality.

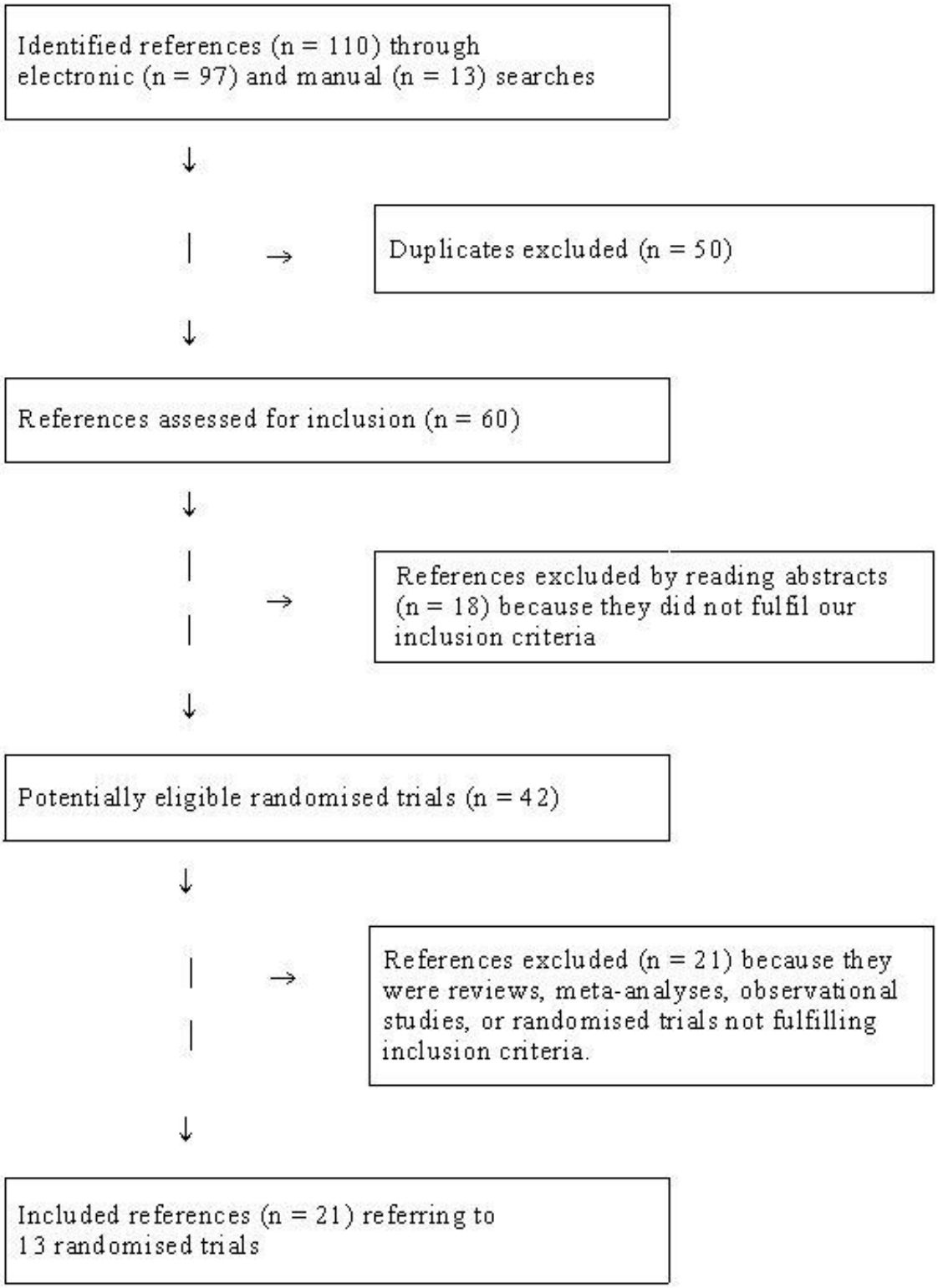
Data extraction
Two reviewers (BAN and LLG) independently extracted data from each trial. Primary investigators were contacted if data were missing. We extracted whether the trial used a parallel or crossover design, washout period between the two periods, methodological quality, type and etiology of the underlying liver diseases, form of hepatic encephalopathy (acute, chronic, subclinical, or fulminant hepatic failure), mean age, proportion of men, number of patients randomised, type, dose and duration of therapy, mode of administration, type of additional interventions, outcomes, and whether the trial assessed cost-effectiveness.

Quantitative data synthesis
All analyses were if possible performed according to the intention-to-treat method, i.e., including all randomised patients irrespective of compliance or follow-up. If patients had missing outcome data, we used the last reported observed response ('carry forward') (Hollis 1999). The statistical package (RevMan Analyses 1.0.1) provided by The Cochrane Collaboration was used. Data from the first period of crossover trials were included. Binary outcomes were expressed as risk difference (RD) and 95% confidence intervals (CI). We used a random effects model (DerSimonian 1986) due to anticipated variability between trials regarding patients and interventions. The presence of statistical heterogeneity was explored by a chi-squared test with significance set at $P < 0.1$. The inconsistency across trials was assessed by I^2 (Higgins 2003). Potential sources of heterogeneity were explored through subgroup analyses with regard to the methodological quality, form and stage of hepatic encephalopathy, trial design, and treatment regimens. We used the test of interaction (Altman 2003) to compare the difference between the estimates of subgroup analyses.

The statistical package STATA was used to assess funnel plot asymmetry indicating the presence of publication and other biases. We used the Egger et al. regression asymmetry test (Egger 1997) on the outcome 'improvement of hepatic encephalopathy'.

DESCRIPTION OF STUDIES

Search results



summarises the literature search. We identified 110 references in The Cochrane Hepato-Biliary Group Controlled Trials Register (n = 22), The Cochrane Central Register of Controlled Trials (CENTRAL) (n = 21), MEDLINE (n = 23), EMBASE (n = 31), and reference lists (n = 13). We excluded 50 duplicates and 18 clearly irrelevant references by reading abstracts. We retrieved 42 references for further assessment. Of these, we excluded 21 because they were reviews, observational studies, or randomised trials that did not fulfil our inclusion criteria. The excluded studies are listed under 'Characteristics of excluded studies', with

reasons for exclusion. The remaining 21 references described 13 randomised trials included in this review. Please see 'Characteristics of included studies' for detailed information and Table 02 for an overview of trials.

Trial characteristics

Design

Of the 13 included trials, 11 were reported in full articles. One trial was reported as a short letter (Klotz 1989) and one as an abstract (Hermant 1991). One trial was reported in Chinese (Zhu 1998) and another in French (Hermant 1991). The remaining 11 trials were available in English. Five trials including 180 patients used a parallel group design (Hermant 1991; Gyr 1996; Lacetti 2000; Zhu 1998; Dursun 2003). The remaining eight trials were crossover trials. In three trials, only patients without clinical improvement during the first study period were crossed over (Pomier 1994; Cadranel 1995; Barbaro 1998). Six of the crossover trials reported a washout period ranging from one hour to one week (median 24 hours). Four trials did not report results from the first treatment period (Kapczinski 1995; Van der Rijt 1995; Gooday 1995; Amodio 1997). Accordingly, most of the data from these trials could not be included.

Patients

A total of 805 patients (67% men) were randomised. The median number of patients in each trial was 20 (range 2 to 527). The mean ages ranged from 44 to 59 years (median 54 years). Patients had cirrhosis (12 trials) or acute or chronic liver disease (Van der Rijt 1995). In the latter trial (Van der Rijt 1995) five patients had encephalopathy in connection with fulminant hepatic failure. Two of the patients were withdrawn after the first study day for liver transplantation. Included patients had subclinical hepatic encephalopathy (Gooday 1995; Kapczinski 1995; Amodio 1997), acute hepatic encephalopathy (Hermant 1991; Lacetti 2000), either subclinical or mild hepatic encephalopathy (Dursun 2003), or either overt acute or chronic hepatic encephalopathy, but no differentiation was made between these two patient categories (seven trials). Of the ten trials assessing overt acute or chronic hepatic encephalopathy, four trials (Klotz 1989; Hermant 1991; Pomier 1994; Barbaro 1998; Lacetti 2000) included only patients with severe encephalopathy (grade III - IV). Two trials included patients with hepatic encephalopathy grade II-IV (Cadranel 1995; Zhu 1998), two trials included patients with grade I-III (Gyr 1996; Dursun 2003), and one trial included patients with grade I-IV (Van der Rijt 1995). The aetiology of cirrhosis was alcohol (37%), hepatitis (58%), or other (5%).

Interventions

All trials compared flumazenil with placebo. Flumazenil was given as a continuous infusion (12 trials), preceded by bolus injections in two trials (Van der Rijt 1995; Gyr 1996). One trial used only bolus injections (Amodio 1997). Patients received flumazenil at a total dose ranging from 0.2 to 19.5 milligram (median 2 milligram). The median duration of treatment was 10 minutes (range one minute to 72 hours). Eight trials reported that patients received additional therapy in both intervention groups (Pomier 1994; Gooday 1995; Van der Rijt 1995; Gyr 1996; Barbaro 1998; Zhu 1998; Lacetti 2000; Dursun 2003). In seven of these trials lactulose was administered in combination with a variety of drugs: saline, glucose, vitamin K, potassium, neomycin, branched-chain amino acids, and antibiotics to patients with sepsis.

Benzodiazepine screening

Seven trials screened blood samples for benzodiazepines at entry (Pomier 1994; Cadranel 1995; Van der Rijt 1995; Gyr 1996; Amodio 1997; Barbaro 1998; Lacetti 2000). The detection limit ranged from 11 to 300 microgram/litre (median 31 microgram/litre). The screening test was negative for all patients in one trial (Amodio 1997). Positive benzodiazepine screening was reported in 14/304 patients randomised to flumazenil (Pomier 1994; Gyr 1996; Barbaro 1998) and 4/283 patients randomised to placebo (Gyr 1996; Barbaro 1998). Two trials reported the result of the screening test for all patients, but did not differentiate between the flumazenil or placebo group (Cadranel 1995; Van der Rijt 1995). Patients with positive benzodiazepine screening were excluded in one trial (Lacetti 2000) and included in five trials (Pomier 1994; Cadranel 1995; Van der Rijt 1995; Gyr 1996; Barbaro 1998).

Outcomes and follow-up

Many of the outcomes we wanted to assess could only be extracted from few or none of the trials. The majority of patients were crossed over (8/13 trials, 625/805 patients) after short treatment and washout periods. Accordingly, in these trials it was only possible to assess short-term responses of the first crossover period at 'end of treatment'. This 'end of treatment' covers an interval of ten minutes to six hours after the last injection of flumazenil/placebo. Outcomes after this time-frame were only assessable in two parallel trials comprising 74 patients; one trial reported follow-up until end of hospitalisation or death (Zhu 1998) and another reported one month follow-up (Gyr 1996).

METHODOLOGICAL QUALITY

All trials were described as randomised, but an adequate method of generating the allocation sequence was reported for only four trials (Gooday 1995; Gyr 1996; Zhu 1998; Barbaro 1998). Treatment allocation was adequately concealed in six trials (Pomier 1994; Cadranel 1995; Gooday 1995; Gyr 1996; Barbaro 1998; Zhu 1998). All trials were double-blind with an adequate description in 12 trials and unclear description in one trial (Klotz 1989). Follow-up was adequately described in five trials (Gooday 1995; Van der Rijt 1995; Gyr 1996; Zhu 1998; Dursun 2003). We classified six trials as having high methodological quality (Pomier 1994; Cadranel 1995; Gooday 1995; Gyr 1996; Barbaro 1998; Zhu 1998).

RESULTS

Compared with placebo, flumazenil had a significant beneficial effect on improvement of hepatic encephalopathy at the end of treatment (risk difference (RD) 0.28; 95% confidence interval (CI) 0.20 to 0.37, eight trials). Flumazenil had no significant effect on recovery (RD 0.13; 95% CI -0.09 to 0.36, two trials), mortality RD 0.01; 95% CI -0.05 to 0.07, ten trials), or adverse events (RD 0.06; 95% CI -0.06 to 0.18, six trials). Trial results on improvement, recovery, and mortality were homogenous. There was significant heterogeneity ($P < 0.0001$) and substantial inconsistency ($I^2 = 83\%$) on the occurrence of adverse events across trials. This heterogeneity was due to the result of the large trial by Barbaro 1998 where none of the 527 patients receiving flumazenil experienced adverse events. In the five other trials, 7/77 patients (9%) given flumazenil experienced adverse events (flushing, nausea, irritability, temporarily palpitations, repetitive clonic movements). There was no heterogeneity when excluding the trial by Barbaro ($P = 0.33$; $I^2 = 14\%$) and this meta-analysis indicated a trend towards more adverse events in the flumazenil group (RD 0.06; 95% CI -0.02 to 0.14, four trials). None of the trials reported that the adverse events caused dose reductions or discontinuation of therapy.

Data regarding time to improvement could only be extracted from two trials (Hermant 1991; Barbaro 1998). Further, Barbaro et al. (Barbaro 1998) reported only this outcome for a subgroup of patients (25% of the patients receiving flumazenil and 3% receiving placebo). The results are highly heterogeneous. Patients given flumazenil in the Barbaro trial (Barbaro 1998) improved within about five minutes, whereas on average it took more than four hours for patients to improve in the Hermant trial (Hermant 1991). Further, patients receiving placebo in the Barbaro trial improved in about six to seven minutes, whereas patients receiving placebo in the Hermant trial improved after an average of 21 hours. These data were considered too heterogeneous to combine.

Subgroup analyses indicated that improvement of hepatic encephalopathy was not significantly associated with methodological quality, trial design, treatment regimens, stage of hepatic encephalopathy at entry, or the presence of exogenous benzodiazepines. However, the subgroup analyses were limited by the small power to detect differences. None of the included trials assessed the quality of life or cost-effectiveness.

A funnel plot assessing the trials effect estimates on improvement of hepatic encephalopathy against sample size revealed no significant funnel plot asymmetry (intercept 1.60; standard error (SE) 1.11; $P = 0.22$).

DISCUSSION

Flumazenil causes short-term improvement of hepatic encephalopathy in patients with cirrhosis and acute or chronic hepatic encephalopathy. It is uncertain how long time this effect lasts. There is no evidence that flumazenil has any significant effect on recovery or survival from hepatic encephalopathy. Included patients had a highly favourable prognosis with a survival rate of 93% in the flumazenil group and 92% in the placebo group. Treatment with flumazenil may be associated with adverse events.

Our results are in accordance with a recently published meta-analysis (Goulenok 2002). This was based on only six studies, of which two (Gyr 1996; Groeneweg 1996) referred to the same trial. Clinical improvement was assessed by meta-analysing four trials (Goulenok 2002), whereas we were able to include eight trials assessing this outcome.

Our systematic review is based on trials with a fair methodological quality. Sixty-three per cent of the trials contributing with data on clinical improvement of hepatic encephalopathy had high quality, but this did not appear to affect the treatment effect. It has to be noted that most of the trials are small except the trial by Barbaro et al. (Barbaro 1998), which had a substantial weight in the present review. It is possible that negative trials exist. Such trials are difficult to identify, because they are more frequently unpublished or are published in less accessible journals (Gluud 1998). However, the funnel plot analysis revealed no evidence of publication bias or other biases (Egger 1997).

All patients included in our meta-analyses had cirrhosis. It was not possible to assess whether the treatment response differed with regard to the type of hepatic encephalopathy, because trials or patients could not be stratified according to the type of hepatic encephalopathy. The majority of trials did not specify the type or did not differentiate between patients with either acute or chronic hepatic encephalopathy. Sensitivity analyses indicated that the treatment response was not associated with the grade of hepatic encephalopathy, but too few patients have been randomised to reliably exclude a potential difference. Further, the treatment response did not appear to be associated with the dose or duration of treatment. Trials using short-term infusion (less than or equal to the median duration of 10 minutes) and lower dose of flumazenil (less than or equal to the median dose of 2 mg) found comparable efficacy of flumazenil than trials using long-term infusion and a higher dose.

A sensitivity analysis excluding patients with positive benzodiazepine screening indicated that treatment response of flumazenil is not related to the presence of exogenous benzodiazepines. There was a variation in the use of screening methods and detection limits. Further, the screening methods were designed to detect the presence of exogenous benzodiazepines only, and not the presence of endogenous benzodiazepine-like compounds. Accordingly, we were unable to evaluate if the effect of flumazenil is correlated with the presence of endogenous benzodiazepine-like substances, with the presence of increased cerebral benzodiazepine receptor availability (Mullen 1990; Avallone 1998; Jalan 2000), or alternatively, some non-specific arousal phenomenon of the drug independent of any interaction with the benzodiazepine receptor.

None of the trials were designed to assess outcomes after the end of treatment. This was primarily due to the fact that most of the trials were crossover trials (8/13) and that the four parallel trials did not report the number of patients improving or recovering after the end of treatment. Many of the included trials reported in various terms that most patients, regardless of their response to flumazenil or placebo, regained consciousness on standard medical therapy for hepatic encephalopathy. One trial reported that most patients who did not respond to flumazenil improved spontaneously within 24 to 48 hours after randomisation (Barbaro 1998). Two trials reported that most patients regained their consciousness within one to five days (Pomier 1994; Zhu 1998). The lack of systematic focus on 'long-term' effects is possibly due to the knowledge, that flumazenil has a rapid onset of action - within one to two minutes - and a short elimination half-life (0.7 to 1.3 hours) (Whitwam 1995). As such, flumazenil has not been expected to have any 'long-term' effects. However, there are some considerations that advocate for a follow-up after the end of treatment. First, having found an improvement rate of 31% at the end of treatment and considering the fluctuating nature of hepatic encephalopathy (Basile 1991) it would have been appropriate to assess the length of time this beneficial effect would last after the end of treatment. Second, intervening and improving the state of consciousness at an early point could affect both the course of hepatic encephalopathy and diminish the occurrence of potential complications and thereby affect the number of patients recovering or surviving after the end of treatment. This review could not demonstrate that flumazenil leads to a higher recovery or survival rate than placebo. There was a remarkably high survival rate in the included trials (93% for the patients receiving flumazenil and 92% for the patients receiving placebo). This reflects most likely both the short follow-up and the result of the included patients being highly selected. Future trials should assess if treatment with flumazenil leads to a sustained improvement or increased recovery or survival.

Our primary analysis indicated that flumazenil did not cause significantly more adverse events. This analysis revealed significant heterogeneity and inconsistency among trial results. Flumazenil may be associated with adverse events, but none of the 13 trials reported adverse events leading to discontinuation of therapy or dose reduction. The presence of adverse events has been reported to occur in 20 to 40 per cent of patients treated with flumazenil for reversal of benzodiazepine intoxication (Hoffman 1993). The discrepancy between these findings and our results may be due to differences between patients suffering from hepatic encephalopathy and patients with benzodiazepine intoxication. It may be difficult to differentiate between the signs and symptoms of benzodiazepine withdrawal and adverse effects of flumazenil.

The assessment of hepatic encephalopathy and the definition of improvement covers a heterogeneous spectrum in the included trials. Some patients were assessed by a modified Glasgow coma scale score (range eight to 27) or a modified portal-systemic encephalopathy score (range three to 14) based on clinical variables. Others were evaluated by gradings of electroencephalogram, or a variety of psychometric tests. Improvement assessed by one method was often not accompanied with improvement assessed by another method. Therefore, when improvement was assessed in several ways we used the data that were clinically most relevant (e.g., the number of patients with improvement on the neurological score instead of improvements in electroencephalogram tracings from the trial by Barbaro et al., and the clinical portal-systemic encephalopathy score instead of the electroencephalogram grading from the trial by Gyr et al.). This heterogeneity in definitions of improvement reflects a general problem within the field of hepatic encephalopathy: the clinical conditions that are summarised under the term 'hepatic encephalopathy' are highly heterogeneous. Accordingly, the methods used to quantitate treatment effects and treatment outcomes are highly variable. In general, the scales and items used for assessing hepatic encephalopathy are arbitrary and not tested for reliability or validity. There is a substantial need for clear definitions and diagnostic criteria of hepatic encephalopathy as well as a reassessment and validation of the various scales and items using sound methodological approaches. A step in this direction has been the recently

published consensus statement regarding hepatic encephalopathy on new terminology, definition, and diagnostic criteria (Ferenci 2002).

Hepatic encephalopathy has a spontaneously fluctuating nature (Basile 1991). Patients' underlying condition and ability to respond to treatment might not remain stable from the first to the second treatment period. Accordingly, the crossover design does not seem appropriate when assessing interventions for hepatic encephalopathy. However, 8 of the 13 trials included in this review were crossover trials. Ideally, data from crossover trials should be analysed taking the pairing into consideration (Elbourne 2002). Due to the spontaneously fluctuating nature of hepatic encephalopathy we had planned a priori to include only data from the first treatment period. This seems even more appropriate considering that in three trials, only patients without clinical improvement during the first study period were crossed over (Pomier 1994; Cadranel 1995; Barbaro 1998) and only two trials had tested for the possibility of a period effect (Kapczinski 1995; Van der Rijt 1995). A subgroup analysis showed that the treatment effect was not associated with the design of the trials. Data from parallel trials were comparable with data from the first treatment period and the unpaired data from both treatment periods in crossover trials.

REVIEWERS' CONCLUSIONS

Implications for practice

Flumazenil causes short-term improvement of hepatic encephalopathy in patients with cirrhosis and hepatic encephalopathy. It is uncertain how long time this effect lasts. There is no evidence that flumazenil has any significant effect on recovery or survival from hepatic encephalopathy. Until this has been demonstrated, flumazenil may be considered for patients with cirrhosis and hepatic encephalopathy, but cannot be recommended for routine clinical use.

Implications for research

Future randomised trials should evaluate if flumazenil has any effect on improvement of hepatic encephalopathy after the end of treatment, recovery from hepatic encephalopathy, and survival of these patients. Further, it should be assessed if the efficacy of flumazenil is different in acute, chronic, or subclinical hepatic encephalopathy or related to the underlying liver disease, or the stage of hepatic encephalopathy at entry. It may also be relevant to assess the potential effects of flumazenil in regard to exogenous and endogenous benzodiazepine concentrations.

Future trials should use a parallel group design, due to the fluctuating nature of hepatic encephalopathy and the need for assessing responses like improvement, recovery, and survival after the end of treatment. Future trials should be adequately powered high-quality trials and report results according to the CONSORT statement (www.consort-statement.org).

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POTENTIAL CONFLICT OF INTEREST

None known.

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SYNOPSIS

Flumazenil causes short-term improvement of hepatic encephalopathy in patients with chronic liver disease

Hepatic encephalopathy refers to changes in mental state, ranging from minor signs of altered brain function to deep coma occurring in patients with liver failure. Hepatic encephalopathy may be caused by an activation of a receptor-complex in the brain. Flumazenil, which inhibits this receptor-complex, might ameliorate the symptoms. This review found that flumazenil leads to a short-term improvement of hepatic encephalopathy in some patients with chronic liver disease and a highly favourable prognosis.

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Amodio 1997
Methods	Crossover trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: adequate, described as double-blind, used placebo. Follow-up: unclear.
Participants	13 patients with cirrhosis and chronic, subclinical hepatic encephalopathy were randomised. Mean age (SD): 54 (7) years. Proportion of men: 77%. Aetioloby of cirrhosis: alcohol (77%), hepatitis (15%), mixed aetiology (alcohol and virus-related) (8%). Precipitating factors: none. Detection of benzodiazepines: benzodiazepine screening by an Emit-Dau technique was performed before the beginning of the experiment (detection limit 300 µg/litre diazepam).The test was negative in all patients.
Interventions	Experimental: bolus of 1 mg flumazenil followed by four bolus injections of 0.5 mg flumazenil every 30 minute (total dose = 3 mg). Control: placebo (saline) according to a similar regimen. Treatment duration: 2.5 hours in each period with a three-day washout period. Additional interventions: not reported.
Outcomes	Clinical outcomes were assessed 30 minutes before and within 30 min after the last intervention.
Notes	We were unable to extract data because the results from the first treatment were not reported.
Allocation concealment	B

Study	Barbaro 1998
Methods	Crossover trial. Generation of the allocation sequence: adequate, using a computer generated list. Allocation concealment: adequate, using "two sets of identical ampoules (active drug or placebo) which were prepared to be administered in a random order according to the randomisation crossover design". Blinding: adequate, described as double-blind, used placebo. Follow-up: inadequate.
Participants	527 patients with cirrhosis and acute (78%) or chronic (22%) hepatic encephalopathy were randomised. Patients were in grade III (50%) or IVa (50%). Mean age: 53 years. Proportion of men: 70%. Aetiology of cirrhosis: hepatitis 59%, alcohol 40%, cryptogenic 1%. Precipitating factors: haemorrhage 67%, sepsis 9%, dehydration 1%, surgery 18%, unknown 3%. Detection of benzodiazepines: blood samples were screened for benzodiazepines using chromatography (detection level >11 µg/l) and gas chromatography mass spectrometry. Benzodiazepines were detected in the serum of seven patients receiving flumazenil and three patients receiving placebo.

Characteristics of included studies

Interventions	Experimental: infusion of 1 mg flumazenil in 20 ml saline solution over 3-5 minutes. Control: placebo according to a similar regimen. Treatment duration: 3-5 minutes in each period with a 3 hour washout period. Additional interventions: all patients received lactulose 30 ml every six hours. Patients with sepsis received antibiotics. After the study periods patients were treated with standard treatment including branched-chain amionacids, lactulose, and neomycin.
Outcomes	Clinical outcomes were assessed 10 minutes before and every 10 minutes up to three hours after drug injection. Maximum follow-up was at least 72 hours following flumazenil/ placebo-infusion.
Notes	Only patients without clinical improvement were crossed over. The trial reported time to recovery in days. Considering that the first crossover period lasted three hours it was not possible to assess the spontaneous recovery rate in each intervention arm during the first crossover period.
Allocation concealment	A

Study	**Cadranel 1995**
Methods	Crossover trial. Generation of the allocation sequence: unclear. Allocation concealment: adequate, using sealed vials from central independent unit. Blinding: adequate, described as double-blind, used placebo. Follow-up: unclear.
Participants	14 patients with cirrhosis and 18 episodes of hepatic encephalopathy (grade II-IV, type not specified) were randomised. Mean age (SD): 55 years (7.7). Proportion of men: 71%. Aetiology of cirrhosis: alcohol 71%, hepatitis B 14%, hepatitis C 14%. Precipitating factors: not reported for patients but for episodes. Detection of benzodiazepines: blood and urine samples were screened for the presence of benzodiazepine using chromatography (detection limit > 11 µg/l). Benzodiazepine screening was positive in three patients.
Interventions	Experimental: continuous intravenous infusion of flumazenil 0.1 mg/ml/min for 10 minutes (total: 1 mg). Control: placebo (sodium edetate 1 mg) according to a similar regimen. Treatment duration: 10 minutes in each period with no washout period. Additional interventions: not reported.
Outcomes	Clinical monitoring and EEG grading were monitored before, during and after the administration of flumazenil or placebo. Maximum follow-up were at least 72 hours after the infusion.
Notes	Only patients without clinical improvement were crossed over. Some data are extracted from a meta-analysis in which the primary author of the trial is a co-author.
Allocation concealment	A

Characteristics of included studies

Study	Dursun 2003
Methods	Parallel group trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: adequate, described as double-blind, used placebo, specifies blinded outcome assessment. Follow-up: adequate.
Participants	40 patients with cirrhosis and subclinical (10 patients) or mild hepatic encephalopathy (grade I-III, type not specified) were randomised. Mean age: 44 years. Proportion of men: 73%. Aetiology of cirrhosis: hepatitis 100%. Precipitating factors: not reported. Detection of benzodiazepines: not reported.
Interventions	Experimental: continuous intravenous infusion of flumazenil 1 mg/h for 5 hours (total dose = 5 mg). Control: placebo (saline) according to a similar regimen. Treatment duration: 5 hours. Additional interventions: all patients received lactulose prior to randomisation.
Outcomes	Clinical outcomes were assessed every half hour for 5 hours. EEG was assessed 1 hour after infusion.
Notes	
Allocation concealment	B

Study	Gooday 1995
Methods	Crossover trial. Generation of the allocation sequence: adequate, generated by random numbers. Allocation concealment: adequate, using sealed envelopes. Blinding: adequate, described as double-blind, used placebo. Follow-up: adequate, no patients dropped out or withdrew from the study.
Participants	10 patients with cirrhosis and subclinical hepatic encephalopathy were randomised. Mean age (SD): 54 (7.4) years. Proportion of men: 80%. Aetiology of cirrhosis: alcohol 60%, hepatitis 20%, primary biliary cirrhosis 10%, cryptogenic 10%. Detection of benzodiazepines: the patients were not screened for the presence of benzodiazepines.
Interventions	Experimental: infusion of 0.2 mg flumazenil Control: placebo according to a similar regimen. Treatment duration: lenght of infusion not reported. Patients were crossed over after one week washout period. Additional interventions: patients received their usual treatment, which consisted of a variety of drugs including lactulose.
Outcomes	Cognitive tests were performed "post-infusion". Follow-up were after end treatment and maximum follow-up after one week.

Characteristics of included studies

Notes	We were unable to extract data on improvement because the results from the first treatment were not reported.
Allocation concealment	A

Study	**Gyr 1996**
Methods	Parallel group trial. Generation of the allocation sequence: adequate, using a computer-generated randomisation list Allocation concealment: adequate, using sealed envelopes. Blinding, adequate, described as double-blind, used placebo. Follow-up: adequate.
Participants	49 patients with cirrhosis and hepatic encephalopathy (grade I-III, type not specified) were randomised. Proportion of men: 69%. Mean age: 55 years. Aetiology of cirrhosis: alcohol 51%, hepatitis 35%, portal vein thrombosis (4%), liver tumour 2%, schistsomiasis 2%, unknown 6%. Precipitating factors: not reported. Detection of benzodiazepines: blood samples were screened for benzodiazepines using high pressure liquid chromatography (detection limit 50 µg/litre). In the flumazenil group 3/28 (11%) were positive versus 1/21 (5%) in the placebo group.
Interventions	Experimental: three sequential bolus injections of flumazenil: 0.4 mg; 0.8 mg; and 1 mg given with one minute intervals followed by continuous intravenous infusion of flumazenil 1mg/h for 3 hours (total dose ? 5.2 mg). Control: placebo injections and infusion according to a similar regimen. Treatment duration: 3 hours. Additional interventions: saline, glucose, lactulose, potassium, and vitamin K.
Outcomes	Clinical grading was performed at 60 minutes intervals during the baseline and post-treatment periods and every 30 minutes during treatment. Patients were followed at least four weeks after the study period.
Notes	
Allocation concealment	A

Study	**Hermant 1991**
Methods	Parallel group trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: adequate, described as double-blind, used placebo. Follow-up: unclear.
Participants	12 patients with cirrhosis and acute hepatic encephalopathy (grade IIIa or EEG grade D or E) were randomised. Proportion of men: not reported. Mean age (SD): 58 (5) years. Aetiology of liver disease: not reported. Precipitating factors: not reported. Detection of benzodiazepines: not reported.

Characteristics of included studies

Interventions	Experimental: injection with flumazenil 0,2 mg/kg for 10 minutes. Control: placebo according to a similar regimen. Treatment duration: 10 minutes. Additional interventions: not reported.
Outcomes	Clinical monitoring and EEG grading were done before, during and after the administration of flumazenil or placebo. EEG grading was monitored at least 90 minutes after injection.
Notes	
Allocation concealment	B

Study	**Kapczinski 1995**
Methods	Crossover trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: adequate, described as double-blind, used placebo. Follow-up: unclear.
Participants	20 patients with cirrhosis and subclinical hepatic encephalopathy were randomised. Proportion of ment: 60%. Mean age: 48 years. Aetiology of cirrhosis: alcohol 50%, primary biliary cirrhosis 25%, autoimmune chronic active hepatitis 10%, cryptogenic cirrhosis 10%, primary sclerosing cholangitis 5%. Precipitating factor(s): not reported. Detection of benzodiazepines: not reported.
Interventions	Experimental: flumazenil 1 ml/min (0.1 mg/min) for 10 min (infusion) followed by 5 ml/min (0.1 mg/min) for 20 min (total dose = 2 mg). Control: placebo (saline infusion) 1 ml/min for 10 min followed by 5 ml/min for 20 min. Treatment duration: 30 minutes in each period with a one-hour washout period. Additional interventions: not reported.
Outcomes	Initially a baseline assessment was performed, followed by infusion of 1 mg flumazenil during 10 minutes. Hereafter a new assessment during the next continuous infusion with 1 mg flumazenil during 20 minutes. Maximum follow-up was at end of treatment.
Notes	We were unable to extract data because the results from the first treatment were not reported.
Allocation concealment	B

Study	**Klotz 1989**
Methods	Crossover trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: unclear, the trial is described as double-blind, but methods of blinding not reported. Follow-up: unclear.

Characteristics of included studies

Participants	Two patients with cirrhosis and chronic hepatic encephalopathy (grade III) were randomised. Proportion of men: not reported. Mean age: not reported. Aetiology of cirrhosis: alcohol 100% Precipitating factors: none. Detection of benzodiazepines: not reported.
Interventions	Experimental: flumazenil 1 mg loading dose over 1 minute. Control: placebo - the regimen not specified. Treatment duration: 1 minute. Additional interventions: not reported.
Outcomes	Coma status was evaluated during a two hours follow-up period after end treatment.
Notes	
Allocation concealment	B

Study	**Lacetti 2000**
Methods	Parallel group trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: adequate, described as double-blind, used placebo. Follow-up: unclear.
Participants	54 patients with cirrhosis and acute hepatic encephalopathy (grade III or IV) were randomised. Proportion of men: 53%. Mean age: 59 years. Aetiology of cirrhosis: hepatitis C: 87%, hepatitis B: 13%. Precipitating factors: gastrointestinal bleeding 57%, sepsis 13%, iatrogen (diuretics) 28%, surgery 2%. Detection of benzodiazepines: urine samples were screened for benzodiazepines using KIMS immunoenzymatic system and confirmation tests were performed by means of high pressure liquid chromatography. Four patients with detectable benzodiazepines were excluded from the study.
Interventions	Experimental: infusion of 2 mg flumazenil in 50 ml saline solution for 5 minutes. Control: Placebo according to a similar regimen. Treatment duration: 5 minutes. The infusion was repeated after three hours if there had been no improvement and immediately in case of relapse of HE symptoms after an initial improvement. Additional interventions: saline, glucose, lactulose enemas, and branched-chain amino acids were permitted.
Outcomes	Neurological assessment was performed before the treatment, at the end of infusion, and then every 30 minutes for the first six hours and every six hours for 24 hours. Clinical improvement was defined as a three point increase in the Glasgow coma score at any time within 24 hours.
Notes	
Allocation concealment	B

Characteristics of included studies

Study	Pomier 1994
Methods	Crossover trial. Generation of the allocation sequence: unclear. Allocation concealment: is borderline, but considered adequate ("two sets of ampoules were prepared to be administered in a random order according to the randomised crossover design"), but the ampoules are not described as identical nor as numbered or coded. Blinding: adequate, described as double-blind, used placebo. Follow-up: unclear.
Participants	21 patients with cirrhosis and hepatic encephalopathy (grade IV, type not specified). Proportion of men: 81%. Mean age: 55 years. Aetiology of cirrhosis: alcohol 62%, hepatitis 24%, cryptogenic 14%. Precipitating factors: none 43%, haemorrhage 33%, sepsis 10%, surgery 10%, dehydration 5%. Detection of benzodiazepines: blood samples were screened for benzodiazepines using gas chromatography mass spectrometry and fluorescence-polariztion immunoassay (detection limit 12 µg/litre). In the flumazenil group 4/11 were positive (two responders and two non-responders). Benzodiazepine screening for the placebo group was not reported.
Interventions	Experimental: infusion of 2 mg flumazenil in 20 ml saline solution over 5 minutes. Control: placebo (saline solution) 20 ml infused over 5 min infusion. Treatment duration: 5 minutes in each period with a 24 hours washout period. Additional interventions: all patients received lactulose 30 ml four times daily. Patients with sepsis received antibiotics, but neomycin or metronidazol were not administered.
Outcomes	Neurological assessment was repeated serially every 15 minute 5½ hours after drug injection. The study drug was considered to have a positive impact if clinical neurological function improved within one hour after administration.
Notes	Only patients without clinical improvement were crossed over.
Allocation concealment	A

Study	Van der Rijt 1995
Methods	Crossover trial. Generation of the allocation sequence: unclear. Blinding: adequate, described as double-blind, used placebo. Follow-up: adequate, the number and reasons for dropouts were clearly described (two patients dropped out due to liver transplantation).

Characteristics of included studies

Participants	18 patients with acute or chronic liver liver disease were randomised. Eleven patients had cirrhosis and chronic hepatic encephalopathy (grade 1-III), two had cirrhosis and acute encephalopathy (gradeI-III), and five had encephalopathy (grade 0-IV) in connection with fulminant hepatic failure. Proportion of men: 39%. Mean age: 50 years. Aetiology of cirrhosis: alcohol 38%, hepatitis 15%, cryptogenic 23%, primary biliary cirrhosis 23%. Precipitating factors: infection 23%, unknown 23%, not reported 54%. Detection of benzodiazepines: blood samples were screened for benzodiazepines using high pressure liquid chromatography (HPLC) (detection limit 50 µg/litre). One patient had positive screening. Four patients had a small peak in the HPLC spectrum, which could not be identified with certainty.
Interventions	The intervention regime was simplified after the first 9 patients were randomised. First part: Experimental: flumazenil 0.1 mg/min for 10 min (1 mg). Four hours later a loading dose of 0.5 mg flumazenil was given followed by infusion of flumazenil 0.25 mg/hour for 72 hours (18 mg) - a total of 19.5 mg. Control: Placebo according to a similar regimen. Treatment duration: 3 days in each period with a 24 hours washout period. Second part: Experimental: flumazenil 1 mg/10 ml given as a loading dose. Control: Placebo (10 ml) given as a loading dose. Treatment duration: 10 minutes in each period with a 24 hours washout period. Additional interventions: standard therapy (protein restriction, lactulose with or without neomycin) was administered to all patients before inclusion in the study.
Outcomes	First part of the study: the degree of encephalopathy was assessed before and 15 minutes after the first injection and after 24, 48, and 72 hours after the beginning of each study periods. Second part: the degree of encephalopathy was assessed before and 15 minutes after drug administration. Maximum follow-up was end of treatment.
Notes	We were unable to extract data on improvement because the results from the first treatment were not reported.
Allocation concealment	B

Study	**Zhu 1998**
Methods	Parallel group trial. Generation of the allocation sequence: adequate, using stratified block randomisation. Allocation concealment: adequate, using sealed, opague, coded envelopes. Blinding: adequate, described as double-blind, used placebo. Follow-up: adequate.
Participants	25 patients with cirrhosis and acute (60%) and chronic (40%) hepatic encephalopathy (grade II-IV) were randomised. Proportion of men: 76%. Mean age: 52 years. Aetiology of cirrhosis: hepatitis 80%, alcohol 12%, cholestasis 4%, liver cancer 4%. Precipitating factors: haemorrhage 52%, large protein intake 25%, infection 8%, surgery 4%, unknown 12%. Detection of benzodiazepines: not reported.

Characteristics of included studies

Interventions	Experimental: infusion of 1 mg flumazenil in 18 ml saline solution over 5 minutes. Control: flumazenil placebo (20 ml saline) according to similar regimen. Treatment duration: 5 minutes. Additional interventions: all patients received branched-chain amino acid-infusion (500 ml 7 %) before treatment with flumazenil/placebo. After trial treatment individual patients received other treatments (not specified) except flumazenil.
Outcomes	Clinical outcomes were assessed after 1.5 and 2.5 hours after the intervention and one time per day until end of hospitalisation or death.
Notes	
Allocation concealment	A

Footnotes:
µg: microgram
EEG: Electroencephalogram

Characteristics of excluded studies

Study	Reason for exclusion
Bansky 1989	Case series in which 14 patients were treated with flumazenil resulting in a transient but distinct improvement in the degree of encephalopathy in 71per cent of the patients.
Burke 1988	Letter, not a randomised clinical trial.
Butterworth 1990	Editorial, not a randomised clinical trial.
Cossar 1997	Review article, not a randomised clinical trial.
Devictor 1995	Case series evaluating the effect of flumazenil on hepatic encephalopathy in nine children with fulminant liver failure. One child improved from grade three to grade two. This effect lasted in 30 minutes. No clinical response was observed in the other children.
Ferenci 1989a	A case report. A patient with portal-systemic encephalopathy refractory to standard therapy was treated with 25 mg flumazenil twice daily (given orally). Before treatment the patient experienced 12 attacks of coma within two years. When treated with flumazenil all signs of encephalopathy abated. When treatment with flumazenil was discontinued the patients became comatose within two days, but when restarted on flumazenil the encephalopathy disappeared.
Ferenci 1989b	Review article, not a randomised trial.
Giger-Mateeva 1999	Randomised trial evaluating the effect of flumazenil on visual event-related potentials in 10 patients with cirrhosis. Only five of the patients had subclinical hepatic encephalopathy.
Golubovic 1999	Case series evaluating the effect of flumazenil in ten patients with hepatic coma. The authors found a clinical improvement in eight patients with in the first six hours after treatment.
Grimm 1988	Case series of 17 patients with hepatic encephalopathy failing to respond to conventional therapy. The patients were treated with various intravenous doses of flumazenil. The treatment was associated with improvement in neurological status in 60 per cent of episodes of hepatic encephalopathy.
Gyr 1991	Review article, not a randomised trial.
Howard 1993	Review article, not a randomised trial.
Jia 1999	Prospective, controlled but not randomised study comparing flumazenil with placebo in 22 patients with cirrhosis and hepatic encephalopathy.

Characteristics of excluded studies

Jones 2001	Study comparing various cognitive sensory functions with standard psychometric tests in patients with cirrhosis without overt encephalopathy. In the study, the authors report the results of a previous trial (Giger-Mateeva 1999) evaluating the effect of flumazenil in 10 patients with cirrhosis. Only 5 of the patients had subclinical hepatic encephalopathy.
Kapczinski 1996	Observational study. Circulating benzodiazepine ligands and binding variables in platelets are measured in alcoholic and nonalcoholic patients with cirrhosis and in controls. The authors find a higher receptor affinity in alcoholic patients than in controls and nonalcoholics, and a correlation between benzodiazepine receptor affinity and some measures of psychomotoric speed.
Marsepoil 1990	Reports a study in a letter. The trial compares 13 patients treated with flumazenil to 12 patients in a control group, who apparently receive no treatment. The authors found no significant difference between the two groups concerning mortality, clinical improvement, or the duration of the encephalopathy. Because the word 'randomised' was not used the study was excluded. A letter has been send to the authors about the methodology of the study.
Meier 1988	Case series comprising of three patients with five episodes of hepatic encephalopathy.
Ozyilkan 1997	Case series comprising of 38 patients. Evoked potential recordings are compared before and after treatment with flumazenil, which showed no significant difference, although four patients showed clinical improvement.
Pidoux 1989	Case series comprising of seven patients suffering from severe hepatic encephalopathy. The study compares EEG recording before and after flumazenil treatment and finds a significant improvement after only a few minutes in six out of seven cases.
Viel 1990	Case series comprising of three patients with acute hepatic encephalopathy stage III or IV. Two patients showed immediate recovery.
Wilkinson 1995	Review article, not a randomised trial.

ADDITIONAL TABLES

Table 01 Search strategies

CHBG-CTR	CENTRAL	MEDLINE	EMBASE	Date of searches
Flumazenil	#1. GABA ANTAGONISTS explode all trees (MeSH) #2. FLUMAZENIL explode all trees (MeSH) #3. ((benzodiazepine next receptor) and (antagonist* or (blocking next agent*))) #4. (gaba and (antagonist* or	#1. explode "GABA-Antagonists"/ all subheadings #2. explode "Flumazenil"/ all subheadings #3. benzodiazepine receptor and (antagonist* or blocking agent*) #4. GABA and (antagonist* or blocking agent*) #5. flumaze*il #6. #1 or #2 or #3 or #4 or #5 #7. explode "Hepatic-Encephalopathy"/ all subheadings	#1. explode "benzodiazepine receptor blocking agent"/ all subheadings #2. explode "4 aminobutyric acid receptor blocking agent"/ all subheadings #3. explode "flumazenil"/ all subheadings #4. benzodiazepine receptor and	All databases were searched January 12, 2004

	(blocking next agent*))) #5. (flumazenil or flumazepil) #6. (#1 or #2 or #3 or #4 or #5) #7. HEPATIC ENCEPHALOPATHY explode all trees (MeSH) #8. (hepatic next encephalopathy) #9. (#7 or #8) #10. (#6 and #9)	#8. hepatic encephalopathy #9. #7 or #8 #10. #6 and #9 #11. random* or blind* or placebo or meta-analysis #12. #10 and #11	(antagonist* or blocking agent*) #5. GABA and (antagonist* or blocking agent*) #6. flumaze*il #7. #1 or #2 or #3 or #4 or #5 or #6 #8. explode "hepatic-encephalopathy"/ all subheadings #9. hepatic encephalopathy #10. #8 or #9 #11. #7 and #10 #12. random* or blind* or placebo or meta-analysis #13. #11 and #12	

Table 02 Overview of randomised trials on flumazenil versus placebo

Study	Study design	Adequate quality	No. of patients	Type of HE	Grade of HE	Dose of flumazenil	Treatment duration	Flumazenil (n/N)	Placebo (n/N)
Amodio 1997	Crossover	No / No / Yes	13	SHE		3 mg	2.5 hours in each period with a three-day washout period.	No data available. No significant effect of flumazenil.	
Barbaro 1998	Crossover	Yes / Yes / Yes	527	AHE + CHE	3-4	1 mg	3-5 minutes in each period with a 3 hour washout period.	66/265	9/262
Cadranel 1995	Crossover	No / Yes / Yes	14	?	2-4	1 mg	10 minutes in each period with no washout period.	6/10	0/8
Dursun 2003	Parallel	No / No / Yes	40	SHE + ?	1-3	5 mg	5 hours	8/20	0/20

Table 02 Overview of randomised trials on flumazenil versus placebo

Gooday 1995	Crossover	Yes / Yes / Yes	10	SHE		0,2 mg	?	No data available. Flumazenil reported to be superior.	
Gyr 1996	Parallel	Yes / Yes / Yes	49	?	1-3	5,2 mg	3 hours	7/28	0/21
Hermant 1991	Parallel	No / No / Yes	12	AHE	3	14 mg	10 minutes	No data available. Flumazenil reported to be superior.	
Kapczinski 1995	Crossover	No / No / Yes	20	SHE		2 mg	30 minutes	No data available. No significant effect of flumazenil.	
Klotz 1989	Crossover	No / No / No	2	CHE	3	1 mg	1 minute	0/1	0/1
Lacetti 2000	Parallel	No / No / Yes	54	AHE	3-4	2 mg	5 minutes	22/28	14/26
Pomier 1994	Crossover	No / Yes / Yes	21	?	4	2 mg	5 minutes in each period with a 24 hours washout period.	5/11	0/10
Van der Rijt 1995	Crossover	No / No / Yes	18	CHE, AHE, fulminant	1-3	19.5 mg	3 days in each period with a 24 hours washout period.	No data available. No significant effect of flumazenil.	
Zhu 1998	Parallel	Yes / Yes / Yes	25	AHE + CHE	2-4	1 mg	5 minutes	3/13	0/12

COVER SHEET

Title	**Benzodiazepine receptor antagonists for hepatic encephalopathy**
Reviewer(s)	**Als-Nielsen B, Gluud LL, Gluud C**

Contribution of reviewer(s)	Bodil Als-Nielsen drafted the protocol for this review, performed the searches, selected trials for inclusion, wrote to authors and pharmaceutical companies, performed data extraction and data analysis, and drafted the systematic review. Lise Lotte Gluud selected trials for inclusion, performed data extraction, and revised the protocol and the systematic review. Christian Gluud revised the protocol, supervised Bodil Als-Nielsen's contributions, and revised the systematic review.
Issue protocol first published	2000/4
Issue review first published	2001/4
Date of most recent amendment	23 February 2004
Date of most recent SUBSTANTIVE amendment	23 February 2004
Most recent changes	**The search was updated in January 2004, and one additional trial was found and included in the review. In the previous version we performed subgroup analyses on two outcomes: 'Number of patients with improvement of hepatic encephalopathy' and 'Number of patients surviving'. In the updated version we performed subgroup analyses on only one outcome ('Number of patients with improvement of hepatic encephalopathy'). Overall, the results and conclusions are not altered in the updated review.**
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	12 January 2004
Date reviewers' conclusions section amended	Information not supplied by reviewer
Contact address	Dr Bodil Als-Nielsen MD The Cochrane Hepato-Biliary Group Copenhagen Trial Unit, Centre for Clinical Intervention Research Copenhagen University Hospital Department 7102, H:S Rigshospitalet Blegdamsvej 9 DK-2100 Copenhagen DENMARK Telephone: +45 3545 7161 E-mail: Bodil.a@ctu.rh.dk Facsimile: +45 3545 7101
Cochrane Library number	CD002798

Editorial group	Cochrane Hepato-Biliary Group
Editorial group code	HM-LIVER

SUMMARY TABLES

01 Flumazenil versus placebo				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients recovering from hepatic encephalopathy at the end of treatment	2	35	Risk Difference (Random) 95% CI	0.13 [-0.09, 0.36]
02 Number of patients showing improvement of hepatic encephalopathy at the end of treatment	8	736	Risk Difference (Random) 95% CI	0.28 [0.20, 0.37]
03 Number of patients surviving at maximum follow-up	10	766	Risk Difference (Random) 95% CI	0.01 [-0.05, 0.07]
04 Number of patients experiencing any adverse event	6	672	Risk Difference (Random) 95% CI	0.06 [-0.06, 0.18]

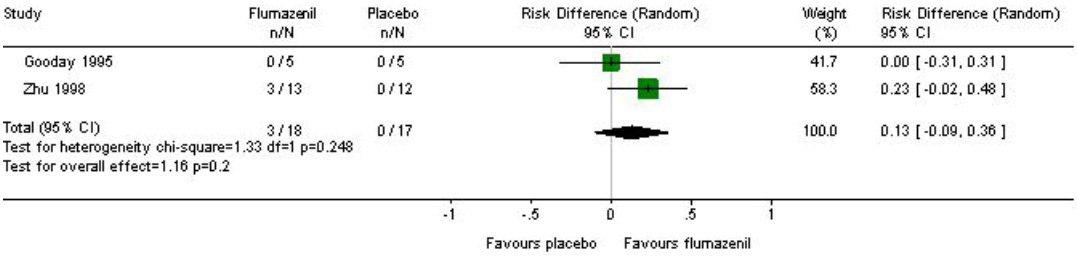
02 Flumazenil versus placebo - subgroup analyses				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Improvement of hepatic encephalopathy - methodological quality	8	736	Risk Difference (Random) 95% CI	0.28 [0.20, 0.37]
02 Improvement of hepatic encephalopathy - grade of hepatic encephalopathy at entry	8	736	Risk Difference (Random) 95% CI	0.28 [0.20, 0.37]
03 Improvement of hepatic encephalopathy - trial design			Risk Difference (Random) 95% CI	Subtotals only
04 Improvement of hepatic encephalopathy - treatment regimens			Risk Difference (Random) 95% CI	Subtotals only
05 Improvement of hepatic encephalopathy - excluding patients a with positive benzodiazepine screening	3	597	Risk Difference (Random) 95% CI	0.19 [0.14, 0.24]
06 Adverse events - excluding the trial by Barbaro	5	145	Risk Difference (Random) 95% CI	0.06 [-0.02, 0.14]

GRAPHS AND OTHER TABLES

Fig. 01 Flumazenil versus placebo

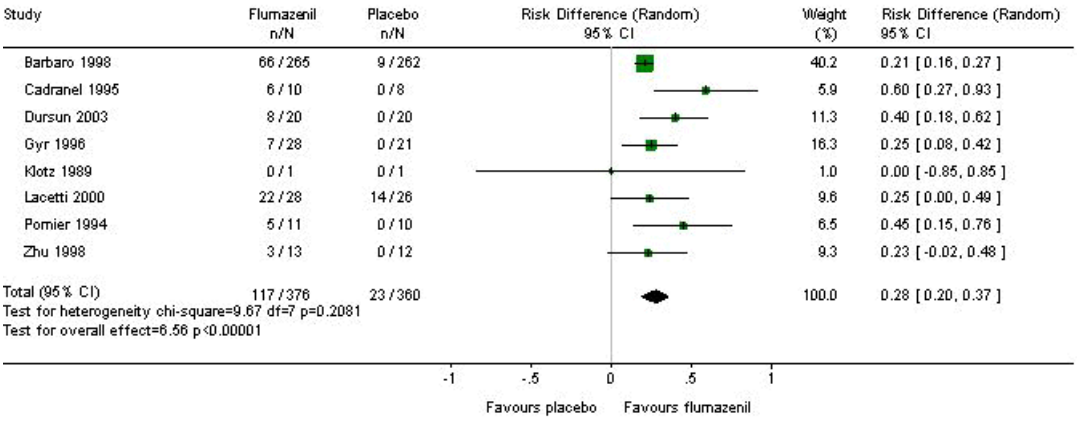
01.01 Number of patients recovering from hepatic encephalopathy at the end of treatment

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 01 Flumazenil versus placebo
Outcome: 01 Number of patients recovering from hepatic encephalopathy at the end of treatment



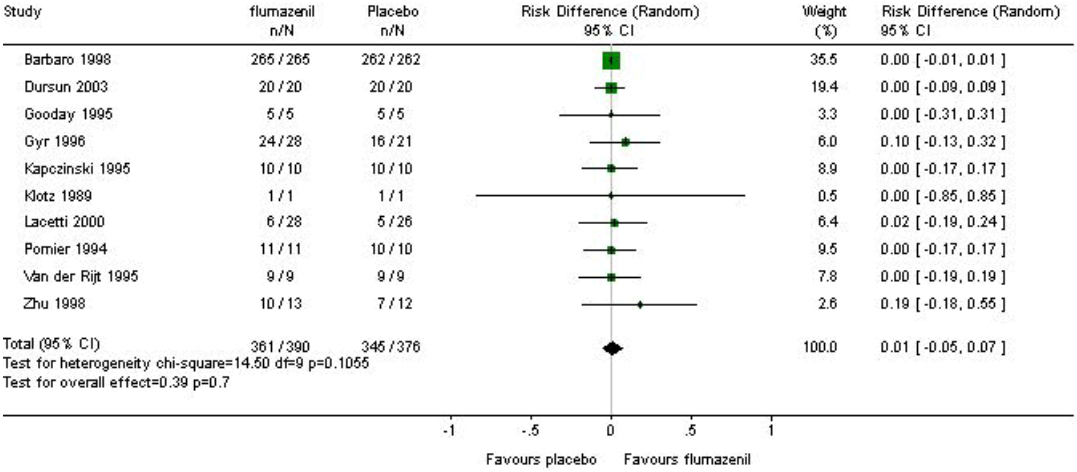
01.02 Number of patients showing improvement of hepatic encephalopathy at the end of treatment

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 01 Flumazenil versus placebo
Outcome: 02 Number of patients showing improvement of hepatic encephalopathy at the end of treatment



01.03 Number of patients surviving at maximum follow-up

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 01 Flumazenil versus placebo
Outcome: 03 Number of patients surviving at maximum follow-up



01.04 Number of patients experiencing any adverse event

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 01 Flumazenil versus placebo
Outcome: 04 Number of patients experiencing any adverse event

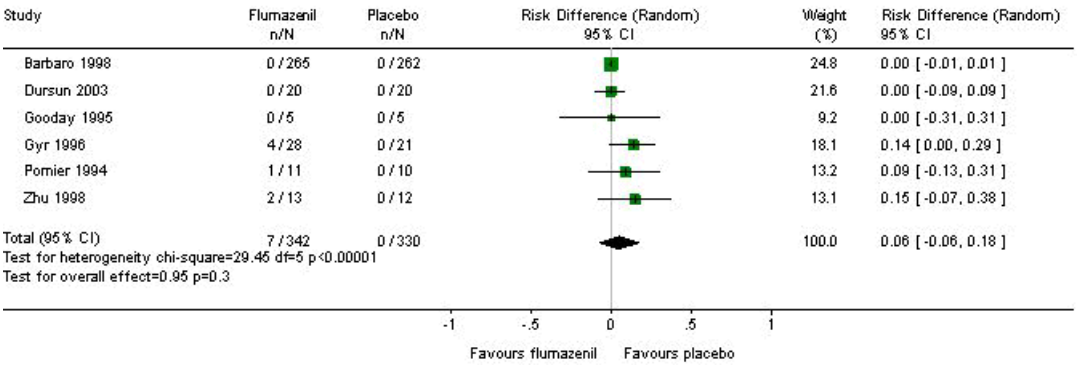
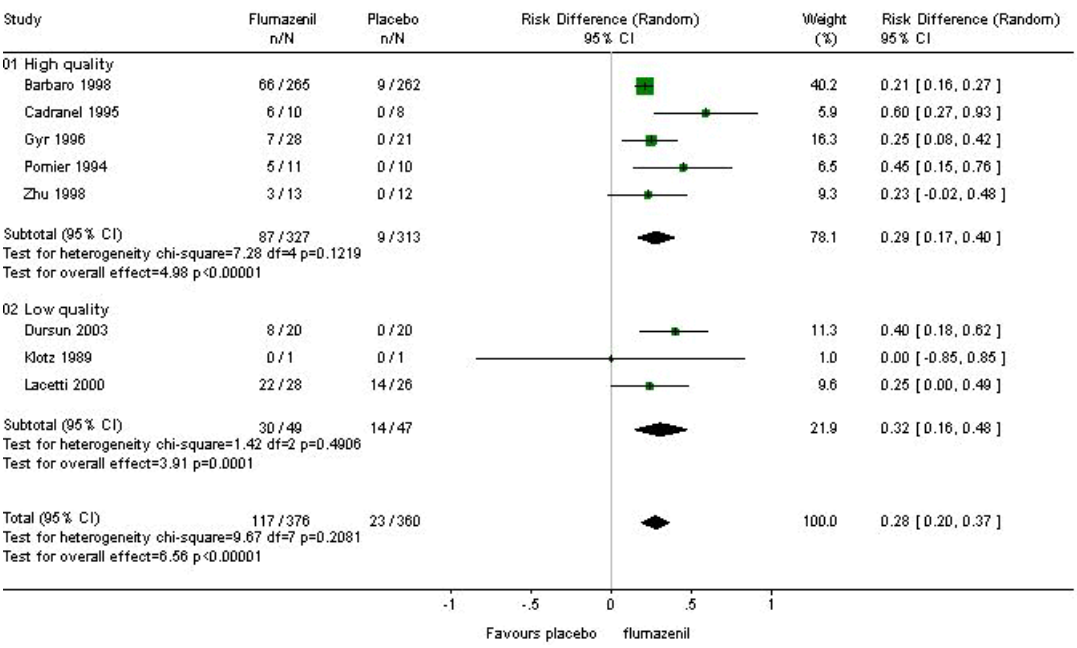


Fig. 02 Flumazenil versus placebo - subgroup analyses

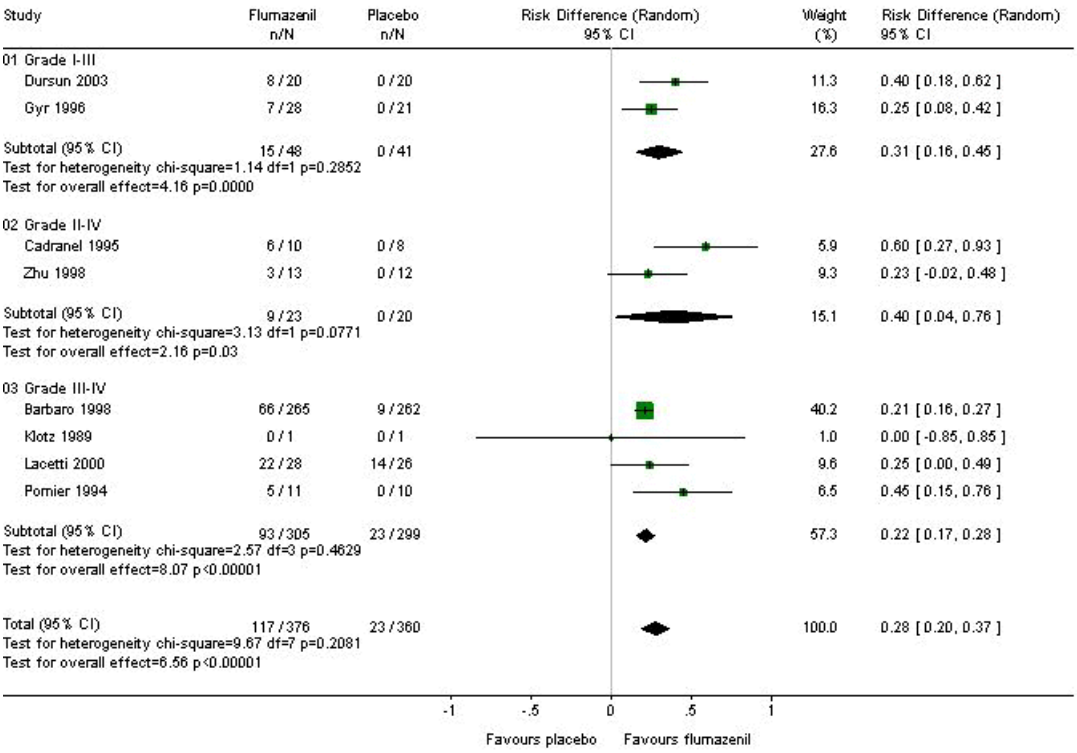
02.01 Improvement of hepatic encephalopathy - methodological quality

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 02 Flumazenil versus placebo - subgroup analyses
Outcome: 01 Improvement of hepatic encephalopathy - methodological quality



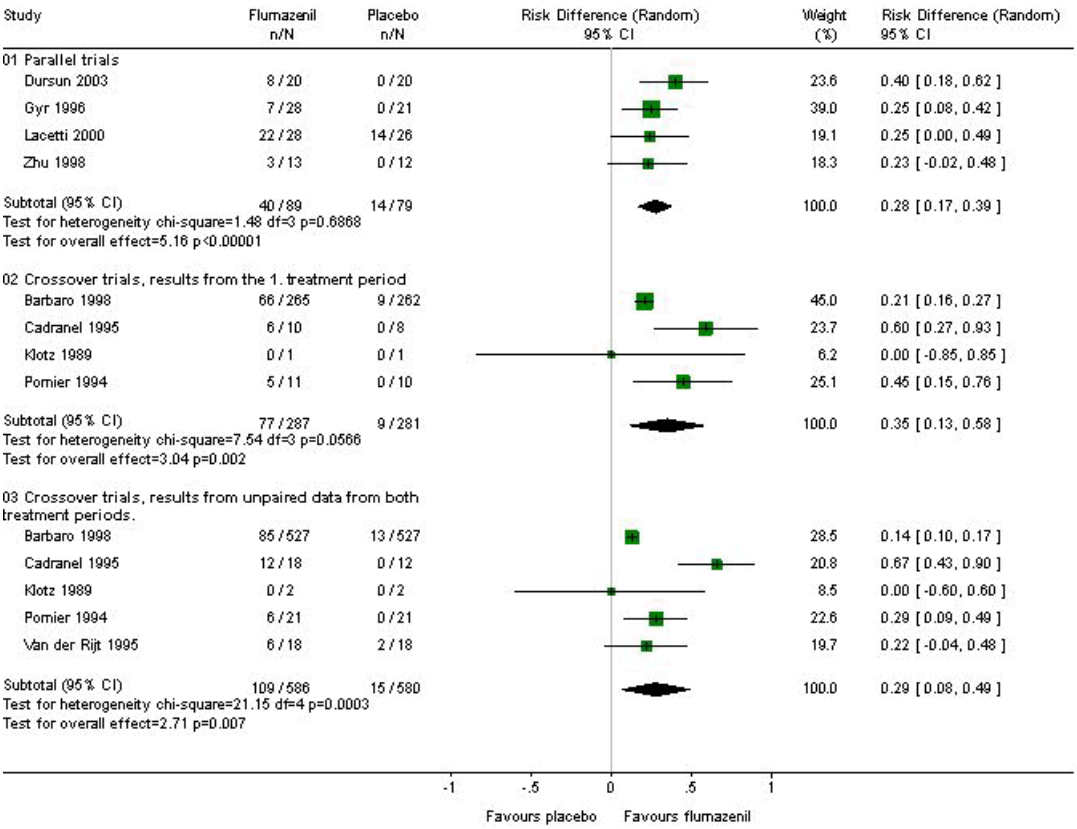
02.02 Improvement of hepatic encephalopathy - grade of hepatic encephalopathy at entry

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 02 Flumazenil versus placebo - subgroup analyses
Outcome: 02 Improvement of hepatic encephalopathy - grade of hepatic encephalopathy at entry



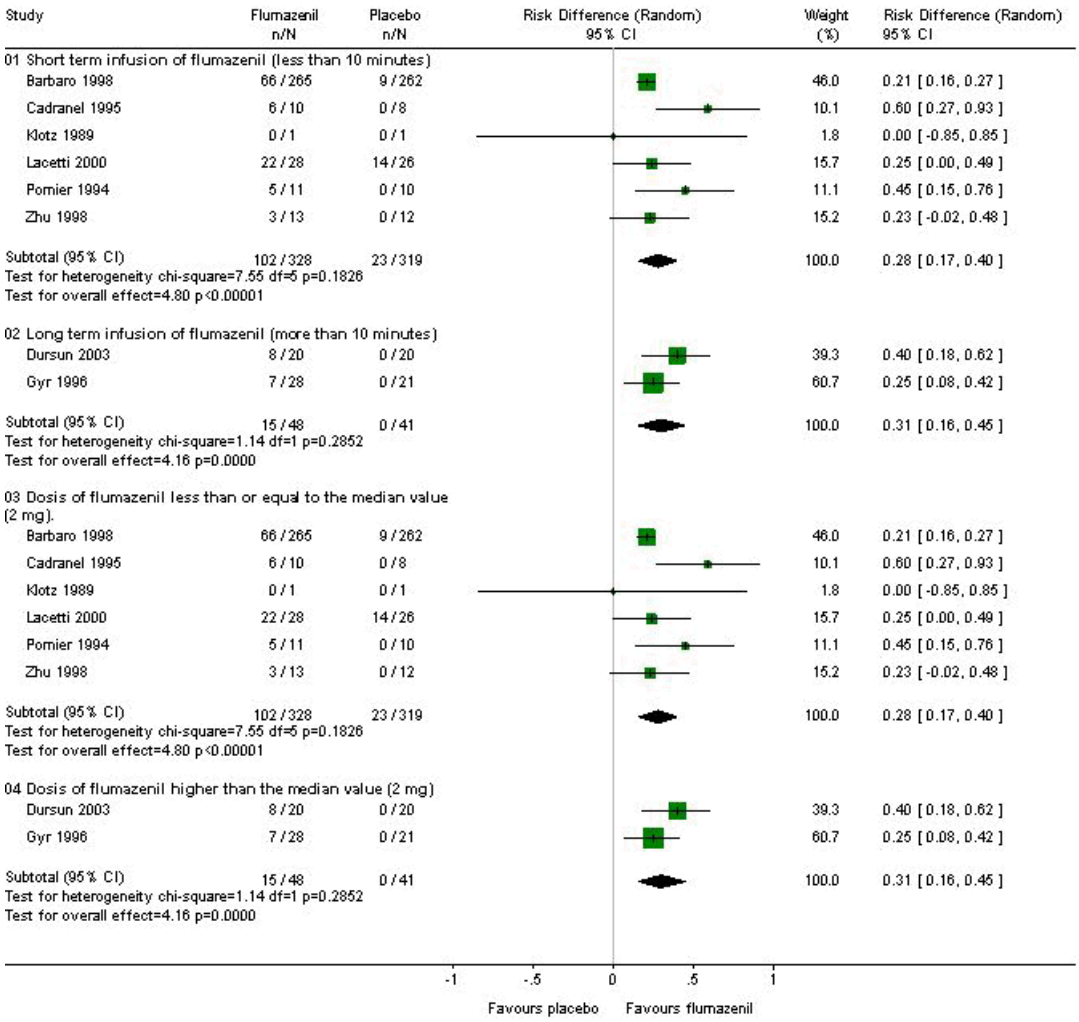
02.03 Improvement of hepatic encephalopathy - trial design

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 02 Flumazenil versus placebo - subgroup analyses
Outcome: 03 Improvement of hepatic encephalopathy - trial design



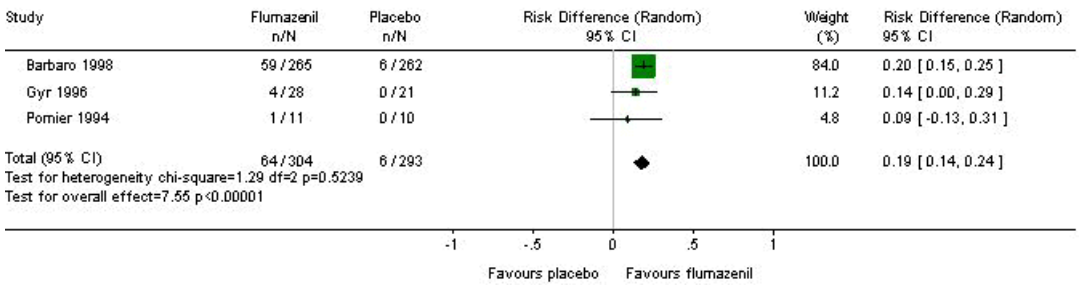
02.04 Improvement of hepatic encephalopathy - treatment regimens

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 02 Flumazenil versus placebo - subgroup analyses
Outcome: 04 Improvement of hepatic encephalopathy - treatment regimens



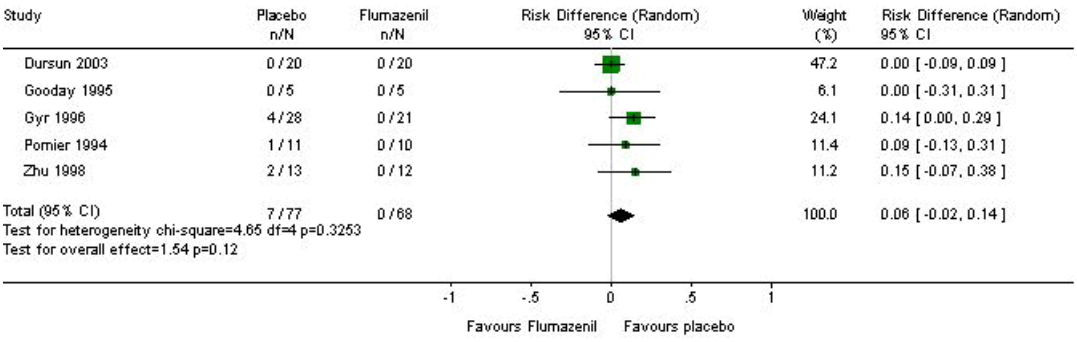
02.05 Improvement of hepatic encephalopathy - excluding patients a with positive benzodiazepine screening

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 02 Flumazenil versus placebo - subgroup analyses
Outcome: 05 Improvement of hepatic encephalopathy - excluding patients a with positive benzodiazepine screening



02.06 Adverse events - excluding the trial by Barbaro

Review: Benzodiazepine receptor antagonists for hepatic encephalopathy
Comparison: 02 Flumazenil versus placebo - subgroup analyses
Outcome: 06 Adverse events - excluding the trial by Barbaro



Paper 3

Branched-chain amino acids for hepatic encephalopathy

Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C

This is a reprint of a Cochrane review, prepared and maintained by the Cochrane Collaboration and published in *The Cochrane Library* 2004, Issue 3

Prepared and produced by:

Update Software Ltd, Summertown Pavilion, Middle Way, Oxford OX2 7LG, UK

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Branched-chain amino acids for hepatic encephalopathy

Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C

This Review should be cited as:
Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C. Branched-chain amino acids for hepatic encephalopathy (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Date of most recent amendment: 26 November 2002
Date of most recent substantive amendment: 19 September 2002

ABSTRACT

Background
Hepatic encephalopathy may be caused by a decreased plasma ratio of branched-chain amino acids (BCAA) to aromatic amino acids. Treatment with BCAA may therefore have a beneficial effect on patients with hepatic encephalopathy.

Objectives
To evaluate the beneficial and harmful effects of BCAA for patients with hepatic encephalopathy.

Search strategy
We identified trials through The Cochrane Hepato-Biliary Group Controlled Trials Register (September 2002), (Issue 3, 2002), MEDLINE (1966-2002/09) and EMBASE (1980-2002/05), manual searches of bibliographies and journals, authors of trials, and pharmaceutical companies.

Selection criteria
Randomised trials comparing BCAA with any kind of control therapy for hepatic encephalopathy were included, regardless of blinding, language, or publication status.

Data collection and analysis
Trial inclusion and data extraction were made independently by two reviewers. Our primary outcome was improvement of hepatic encephalopathy. Statistical heterogeneity was tested using random effects and fixed effect models. Binary outcomes are reported as risk ratios (RR) based on a random effects model.

Main results
Eleven randomised trials (556 patients) assessing BCAA versus carbohydrates, neomycin/lactulose, or isonitrogenous control were included. The median number of patients in each trial was 55 (range 22 to 75). Follow-up after treatment was reported in four trials (median 17 days (range 6 to 30 days)). Compared to the control regimens, BCAA significantly increased the number of patients improving from hepatic encephalopathy at the end of treatment (risk ratio (RR) 1.31, 95% confidence interval (CI) 1.04 to 1.66, nine trials). We found no evidence of an effect of BCAA on survival (RR 1.06, 95% CI 0.98 to 1.14, eight trials) or adverse events (RR 0.97, 95% CI 0.41 to 2.31, three trials). Sensitivity analyses indicated that methodological quality had significant impact on the results. We found no evidence of an effect of BCAA on improvement of hepatic encephalopathy in trials with adequate generation of the allocation sequence (RR 1.01, 95% CI 0.84 to 1.23, three trials), adequate allocation concealment (RR 1.09, 95% CI 0.89 to 1.33, five trials), or adequate double-blinding (RR 1.20, 95% CI 0.83 to 1.73, three trials).

Reviewers' conclusions
We did not find convincing evidence that BCAA had a significant beneficial effect on patients with hepatic encephalopathy. The trials performed in this field were small with short follow-up and most had low methodological quality.

BACKGROUND

Hepatic encephalopathy is the term given to an otherwise unexplained altered mental status in patients with acute or chronic hepatic failure (Gitlin 1996). It is characterised by changes in mental state including a wide range of acute or chronic neuropsychiatric symptoms ranging from minor not readily discernible signs of altered brain function, overt psychiatric and/or neurological symptoms to deep coma (Conn 1979; Blei 1999).

Acute hepatic encephalopathy involves an abrupt onset of neuropsychiatric symptoms in patients with chronic liver disease. Acute hepatic encephalopathy may be idiopathic or precipitated by one or more causes including infections, gastrointestinal bleeding, electrolyte or acid-base disturbances, constipation, medications, hypo- or hyperglycaemia, renal dysfunction, large protein meals, alcohol withdrawal, or another superimposed acute liver disease.

Chronic hepatic encephalopathy involves persistent neuropsychiatric dysfunction in patients with chronic liver disease. The onset is usually insidious and the dysfunction may be clinically overt (i.e., chronic hepatic encephalopathy) or only demonstrable by psychometric testing (i.e., minimal hepatic encephalopathy also known as latent or subclinical encephalopathy).

Fulminant hepatic failure is a severe stage of hepatic functional deterioration in patients without underlying liver disease. The main clinical features are hepatic encephalopathy and direct symptoms of liver cell damage, mainly jaundice and coagulation disorders (Bernuau 1999).

Hepatic encephalopathy is reversible and can exhibit a fluctuating course. If the underlying liver dysfunction improves or if the liver is replaced by a functioning liver transplant, the symptoms of hepatic encephalopathy will improve or disappear. With regard to acute hepatic encephalopathy, an intervention directed against the precipitating cause(s) will lead to improvement or disappearance of acute hepatic encephalopathy. This reversibility suggests that hepatic encephalopathy is a metabolic problem secondary to liver dysfunction.

One of the hypothesised metabolic dysfunctions in hepatic encephalopathy is a derangement in the balance of amino acids (Fischer 1971; Morgan 1990). Brain neurotransmitter synthesis is regulated by the central nervous system concentration of precursor amino acids. Circulating plasma concentrations of aromatic amino acids (AAA) (tyrosine, phenylalanine, and tryptophan) are increased in liver disease, perhaps due to impaired hepatic deamination. Plasma concentrations of branched-chain amino acids (BCAA) (valine, leucine, and isoleucine) are often decreased in liver disease, perhaps due to increased skeletal muscle and kidney catabolism. Accordingly, the normal plasma ratio of BCAA/AAA of about 3.5 falls to about 1.0 in patients with cirrhosis (Gitlin 1996). AAA and BCAA share a common transport mechanism into the central nervous system. As a consequence of the changed plasma ratio, the AAA will have easier access to the central nervous system where they may be metabolised to false neurotransmitters (octopamine and phenylethanolamine) (Capocaccia 1979), with the consequent neuropsychiatric syndrome (Fischer 1971; Soeters 1976). If this false neurotransmitter hypothesis is true, provision of BCAA could have a beneficial effect on patients with hepatic encephalopathy. Further, since malnutrition is a common finding in patients with chronic liver disease and hepatic encephalopathy, the provision of BCAA could have a further benefit simply as an energy substrate.

Several randomised trials and reviews have assessed the beneficial and harmful effects of BCAA for patients with hepatic encephalopathy. Three meta-analyses (Tygstrup 1984; Naylor 1989; Gluud 1991) including trials of parenteral BCAA provided to patients with acute hepatic encephalopathy have been published. Naylor et al concluded that BCAA increased recovery rates from hepatic encephalopathy but had uncertain effects on mortality. The two briefer meta-analyses agreed that BCAA had no effect on mortality (Tygstrup 1984; Gluud 1991). In addition, two non-quantitative reviews have been published (Erikkson 1989; Fabbri 1996). The first included trials of either enteral or parenteral BCAA in patients with acute or chronic hepatic encephalopathy. This review concluded that the majority of trials provided little evidence that BCAA were of benefit (Erikkson 1989). The other review only included trials of enteral BCAA in patients with chronic hepatic encephalopathy and concluded that BCAA may be proposed for patients with advanced cirrhosis who are intolerant to alimentary proteins (Fabbri 1996). Although these previous assessments have reached disparate conclusions, a recent consensus statement (Plauth 1997) implied that BCAA may have a beneficial effect on patients with hepatic encephalopathy.

OBJECTIVES

To evaluate the beneficial and harmful effects of branched-chain amino acids (BCAA) or BCAA-enriched interventions for patients with hepatic encephalopathy.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

The review included all randomised trials, irrespective of blinding, publication status, or language. Data from the first period of crossover trials were included. Unpublished trials were included if the methodology and data could be accessed in written form.

We excluded trials in which patients were allocated by a quasi-random method, e.g., day of birth or date of admission.

Types of participants

We included patients with hepatic encephalopathy in connection with acute or chronic liver disease or fulminant hepatic failure. Patients of either gender, any age, or any ethnic origin were included irrespective of the etiology of the liver disease or the factors precipitating the hepatic encephalopathy.

Types of intervention

The experimental intervention could be branched-chain amino acids (BCAA) or BCAA-enriched preparations administered in any mode, dose, or duration with or without other nutritive sources. The control group could be no nutritional support, placebo support, isocaloric support, isonitrogenous support, or other interventions with a potential effect on hepatic encephalopathy (e.g., lactulose or neomycin).

Types of outcome measures

Our primary outcome measure was:

- Improvement of hepatic encephalopathy - number of patients improving from hepatic encephalopathy using the definitions of the individual trials. Improvement was assessed at the end of treatment and at maximum follow-up (continued improvement).

Our secondary outcome measures were:

- Time to improvement of hepatic encephalopathy - the number of hours/days with hepatic encephalopathy from the time of randomisation to improvement.
- Survival - number of patients surviving at the end of treatment and at maximum follow-up according to the individual trial.
- Adverse events - number and types of adverse event defined as any untoward medical occurrence in a patient, which did not necessarily have a causal relationship with the treatment (ICH-GCP 1997).

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (September 2002) and The Cochrane Controlled Trials Register (Issue 3, 2002 using the terms 'branched chain' and ('hepatic encephalopathy' or 'liver disease' or cirrhosis'). We searched MEDLINE (1966-2002/09) using the terms 'branched chain' and ('hepatic encephalopathy' or 'liver disease' or cirrhosis') and (trial or random* or placebo). EMBASE (1980-2002/05) was searched using the terms 'branched chain' and ('hepatic encephalopathy' or 'liver disease' or cirrhosis') and ('controlled study' or 'clinical trial' or 'random*' or 'placebo' or 'blind').

Further trials were identified by one of the reviewers (RLK), who has performed a text search of the medical literature looking for randomised clinical trials dealing with nutritional support. We identified trials through Index Medicus (approximately from 1965 to the present under the topics 'enteral nutrition, fat emulsions, intravenous, food formulated, nutrition assessment, nutrition disorder, parenteral nutrition, parenteral nutrition home, parenteral nutrition total'), reference lists of all pertinent articles thus identified, abstracts of annual meetings of AASLD/AGA since 1975 and specific searches of selected medical journals (Gastroenterology, Hepatology, Journal of Parenteral Nutrition (JPEN), Annals of Internal Medicine, New England Journal of Medicine, Lancet).

We wrote to the principal authors of the identified trials and the pharmaceutical companies involved in the production of BCAA and inquired about additional trials of which they were aware. Further trials were identified through reference lists of relevant articles.

METHODS OF THE REVIEW

Selection of trials for inclusion
Decisions on which trials to include were taken independently by two contributors (BAN and RLK) who were unblinded with regard to the names of the authors, investigators, institution, source, and results. Disagreements were resolved by discussion. Excluded trials were listed with the reason for exclusion.

Methodological quality
Methodological quality was defined as the confidence that the design and report will restrict bias in the intervention comparison (Moher 1998). According to empirical evidence (Schulz 1995; Moher 1998; Kjaergard 2001; Jüni 2001), we assessed the methodological quality by the generation of the allocation sequence, allocation concealment, and double blinding (Table 01).

Data extraction
Standardised extraction sheets were designed and pilot tested before use. Two reviewers (BAN and RLK) extracted data independently from the included trials. The authors of the trials were approached to specify the following data, had they not been reported clearly in the article:

- Trial characteristics
Methodological quality. Whether the trial used a parallel or crossover design. Number of intervention arms. Number of patients with missing data. Length of follow-up.

- Patient characteristics
Number of patients randomised to each intervention arm, mean (or median) age, number of males, form and stage of hepatic encephalopathy, mean duration of hepatic encephalopathy at randomisation, type of underlying liver disease, factors precipitating acute hepatic encephalopathy.

- Intervention characteristics
Type and dose of experimental and control intervention, duration of therapy, mode of administration. Concomitant nutritive regimens. Type and dose of additional interventions.

- Outcomes
All outcomes were extracted from each trial. The method by which hepatic encephalopathy was defined and assessed.

Statistical methods
All analyses were performed according to the intention-to-treat method including all randomised patients irrespective of compliance or follow-up. If patients had missing outcome data, we used the last reported observed response (carry forward) (Hollis 1999). We assessed the effect of missing data in 'best-case' and 'worst-case' intention-to-treat analyses using the outcomes 'number of patients improving at the end of treatment ' and 'number of patients surviving at maximum follow-up'. In the 'best-case-scenario' analyses, patients with missing outcome data were considered as successes in the BCAA group and as failures in the control group. In the 'worst-case-scenario' analyses, patients with missing outcome data were considered as failures in the BCAA group and successes in the control group.

The statistical package (MetaView of RevMan) provided by The Cochrane Collaboration was used. Binary outcomes were expressed as relative risks (RR) with 95% confidence intervals (CI). Continuous outcomes were expressed as weighted mean difference (WMD) with 95% CI. We used a random effects model (DerSimonian 1986) due to anticipated variability between trials regarding patients, interventions, and concomitant regimens. To assess the robustness of the results, analyses were also performed using a fixed effect model (DeMets 1987). In case of discrepancies, results from both models were reported. Otherwise only results from the random effects model were reported. The presence of statistical heterogeneity was explored by the Chi-square test with significance set at $P < 0.1$. Possible sources of heterogeneity were explored by sensitivity analyses.

Sensitivity analyses were performed to assess if improvement of hepatic encephalopathy or survival was associated with methodological quality, form of hepatic encephalopathy (acute, chronic, minimal, or fulminant hepatic failure), stage of hepatic encephalopathy at entry, mode of BCAA administration, dose and duration of BCAA, and control therapies. Finally, a distinction was made between patients with endstage liver disease and patients who developed hepatic encephalopathy partly from iatrogenic procedures such as porto-systemic shunting.

The statistical package Stata was used to assess funnel plot asymmetry indicating the presence of publication and other biases. We used two tests to assess funnel plot assymmetry, the Begg and Mazumdar adjusted rank correlation test (Begg 1994) and the Egger et al regression asymmetry test (Egger 1997). We used 'improvement of hepatic encephalopathy' as the outcome.

For a summary of changes to the protocol (Gluud 1997) please see 'Whats New'.

DESCRIPTION OF STUDIES

Search results
We identified a total of 413 references through electronic searches of The Cochrane Hepato-Biliary Group Controlled Trials Register (n = 153), The Cochrane Controlled Trials Register (n = 68), MEDLINE (n = 49), and EMBASE (n = 143). We excluded 177 duplicates and 122 clearly irrelevant references through reading abstracts. An additional 48 references were identified through manual searches. Accordingly, 162 references were retrieved for further assessment. Of these, we excluded 53 because they were reviews, meta-analyses, or observational studies and 74 randomised trials that did not fulfil our inclusion criteria. The excluded studies are listed under 'Characteristics of excluded studies' with reasons for exclusion. The remaining 35 references referred to 18 randomised trials, which fulfilled our inclusion criteria. However, we could not extract relevant data from seven trials and the authors of the trials did not respond to our request for additional information. These trials are listed under 'Studies awaiting assessment'.

In the present review, we included 11 trials. Ten trials were described in 20 full paper articles and seven abstracts. One trial was only published as an abstract, but the pharmaceutical company sponsoring the trial gave an additional report. Details of the trials are shown in the table 'Characteristics of included studies'. Seven trials used a parallel group design, two trials a cross-over design, and two trials used a combined cross-over and parallel group design.

Patients
A total of 556 patients (68% male) were randomised in the 11 trials. The median number of patients in each trial was 55 (range 22 to 75). The mean ages in these trials ranged from 50 to 61 years (median 56 years). Three patients had fulminant hepatic failure. All other patients had cirrhosis. The etiology of the cirrhosis was alcohol (52%), hepatitis (21%), miscellaneous (12%), and unreported (5%). The patients had acute hepatic encephalopathy (seven trials), chronic hepatic encephalopathy (two trials), or minimal hepatic encephalopathy (two trials). Precipitating factors of acute hepatic encephalopathy were reported in six trials (307 patients): gastrointestinal bleeding (23%), infection (24%), unknown reasons (23%), diuretics (12%), protein overload (3%), and hypokalemia (2%).

Intervention regimens
Trials of acute hepatic encephalopathy used parenteral administration of pure BCAA (one trial) or BCAA-enriched amino acid solutions (six trials). Trials of chronic or minimal hepatic encephalopathy used enteral administration of pure BCAA (three trials) or BCAA-enriched diet (one trial). The median amount of BCAA was 28 gram/day (range 11 to 57 gram) and the median duration of treatment was seven days (range four to 90 days).

The control therapies were glucose (one trial), isonitrogenous control (four trials), neomycin or lactulose (five trials), or placebo (one trial).

Concomitant nutritive regimens

Administration of BCAA and control therapies was in all trials accompanied by special nutritive regimens (see 'Characteristics of included studies'). Although these differed among the included trials comparable regimens were given to the BCAA and control groups within each trial. The five trials assessing BCAA versus neomycin or lactulose administered intravenous glucose or dextrose as the concomitant nutritive regimen, and in two of these trials patients also received a diet. One trial administered a combination of intravenous glucose and lipid as the nutritional support. In other trials patients received a diet composed of 0.7 to 1.0 gram of protein/kg/day (four trials), or the usual diet without protein restriction (one trial). Accordingly, overall the BCAA and control group received equicaloric regimens and in four trials there was also made an effort to provide equinitrogenous regimens to both groups.

Additional therapy

Ten trials reported that additional therapy was given to patients in both intervention groups if necessary. In six of these trials lactulose was administered in combination with a variety of drugs: potassium and electrolytes, diuretics, blood transfusions, insulin, vitamins, and antibiotics. In one trial all patients received lactulose.

Outcomes

At least six scoring systems were used to assess hepatic encephalopathy (e.g., Glasgow coma scale, PSE-index, psychometric tests, or clinical grading according to Adam-Foley, Conn and Lieberthal, Benhamou, or Sherlock). We decided post hoc to assess improvement rather than recovery. This was due to a substantial heterogeneity in the definition of 'recovery' ranging from no definition (one trial), recovery to grade 0 to 1 (two trials) to full recovery (three trials). The remaining five trials assessed improvement rather than recovery. In four trials, patients were followed after treatment (median 17 days; range six to 30 days).

METHODOLOGICAL QUALITY

All trials were described as randomised, but only three trials (27%) reported adequate generation of the allocation sequence. Five trials (45%) reported adequate allocation concealment. Five trials (45%) were double-blind. Six trials (55%) gave adequate descriptions of dropouts and withdrawals. Two trials (18%) reported a sample size estimation.

RESULTS

Improvement of hepatic encephalopathy

A total of 161/274 (59%) improved at the end of treatment in the BCAA group versus 105/254 (41%) in the control group. This difference was significant (risk ratio (RR) 1.31, 95% confidence interval (CI) 1.04 to 1.66, nine trials). We were unable to extract the number of patients with continued improvement from any of the included trials.

Improvement was assessed by the number connection test in three trials. We found no significant effect of BCAA when summarising the post-treatment values of this test (weighted mean difference (WMD) 8 seconds, 95% CI -30 to 46 seconds). There was significant intertrial heterogeneity (P = 0.013) perhaps due to variability regarding the form of hepatic encephalopathy (chronic and minimal hepatic encephalopathy). There was no heterogeneity when limiting meta-analysis to the two trials on minimal hepatic encephalopathy (P = 0.49), but the pre-treatment values of the number connection test were skewed in favour of the control group. Summarising these two trials showed a significant negative effect of BCAA (WMD 25.03 seconds, 95% CI 3.07 to 46.98 seconds).

Time to improvement of hepatic encephalopathy

There was no significant effect of BCAA on time to improvement (WMD -14 hours, 95% CI -38 to 10 hours, three trials). There was significant intertrial heterogeneity (P = 0.011) primarily due to a positive result based on a post-hoc analysis in one trial. The fixed effect model analysis showed a significant beneficial effect of BCAA (WMD -14 hours, 95% CI -25 to -3 hours).

Survival

A total of 196/239 (82%) survived at the end of treatment in the BCAA group versus 171/222 (77%) in the control group. This difference was not significant (RR 1.05, 95% CI 0.98 to 1.12, eight trials). We could extract data from two trials on survival after the end of treatment. Combining survival data regardless of the window of follow-up showed no significant difference (178/239 (74%) survived in the BCAA group versus 152/222 (68%) in the control group, RR 1.08, 95% CI 0.98 to 1.14, eight trials).

Adverse events

The adverse events were partly described and included oliguria and increasing ascites. In the BCAA group 9/84 (11%) experienced an adverse event versus 9/81 (11%) in the control group. Accordingly, BCAA did not significantly increase the risk of adverse events (RR 0.97, 95% CI 0.41 to 2.31, three trials).

Sensitivity analyses

- Methodological quality

The stratification of trials according to adequate generation of the allocation sequence, allocation concealment, or double blinding suggested that methodological quality had significant impact on the results. In trials with adequate generation of the allocation sequence, BCAA had no significant effect on improvement of hepatic encephalopathy (RR 1.01, 95% CI 0.84 to 1.23, three trials). In trials with unclear generation of the allocation sequence, BCAA had a significant beneficial effect

on improvement of hepatic encephalopathy (RR 1.60, 95% CI 1.24 to 2.06, six trials). Accordingly, the estimated effect of BCAA on improvement of hepatic encephalopathy was significantly more positive in trials with unclear compared to trials with adequate generation of the allocation (P = 0.01). Likewise, trials with adequate allocation concealment found no significant effect of BCAA on improvement (RR 1.09, 95% CI 0.89 to 1.33, five trials) whereas trials with unclear allocation concealment showed a significant positive effect of BCAA (RR 1.66, 95% CI 1.16 to 2.38, four trials). Accordingly, the estimated effect of BCAA on improvement of hepatic encephalopathy was significantly more positive in trials with unclear compared to trials with adequate allocation concealment (P = 0.05). The same trend, although not statistically significant, was seen for double-blinding. Trials with adequate double-blinding found no significant effect of BCAA on improvement (RR 1.20, 95% CI 0.83 to 1.73), whereas trials with inadequate double-blinding found a significant effect (RR 1.42, 95% CI 1.00 to 2.02).

The same trend regarding an association between methodological quality and effect of BCAA was seen in the survival analyses. BCAA had no significant effect on survival in any of the sensitivity analyses combining trials with adequate methodological components.

- Form of hepatic encephalopathy and mode of BCAA administration

We assessed if there was a different effect of BCAA in acute or chronic hepatic encephalopathy or in enteral/parenteral administration. However, all trials on acute hepatic encephalopathy administered BCAA parenterally (n = 7) and all trials on chronic hepatic encephalopathy administered BCAA enterally (n = 2). In trials on acute hepatic encephalopathy, parenteral BCAA had a significant effect on improvement of hepatic encephalopathy regardless of which model (fixed or random) was used (RR 1.17, 95% CI 1.00 to 1.36). In trials on chronic hepatic encephalopathy, both models imply a beneficial effect of enteral BCAA. This effect was significant using the fixed effect model (RR 2.89, 95% CI 1.58 to 5.27, P = 0.001), but did not reach statistical significance when a random effects model was applied (RR (random) 3.08, 95 CI 0.97 to 9.76, P = 0.06). There was no heterogeneity in this analysis (P = 0.12). Comparing the effect of BCAA in acute and chronic hepatic encephalopathy revealed discrepancies depending on which model was applied. A significantly higher number of patients with chronic hepatic encephalopathy improved compared to the number of patients improving from acute hepatic encephalopathy when a fixed effect model was applied. However, the difference did not reach statisitical significance when a random effects model was applied.

BCAA had no significant effect on survival when given parenterally to acute hepatic encephalopathy or enterally to chronic hepatic encephalopathy

- 'Best-case' and 'worst-case' analyses

With regard to the number of patients improving, the best-case analysis showed a significant beneficial effect of BCAA. In the worst-case analysis 161/274 (59%) improved in the BCAA group versus 120/254 (47%) in the control group. This difference appeared to be significant using the fixed effect model (RR 1.20, 95% CI 1.03 to 1.41, P = 0.02) but did not reach statistical significance when a random effects model was applied (RR 1.18, 95% CI 0.98 to 1.43, P = 0.08).

With regard to the number of patients surviving, the best-case analysis showed a trend towards a beneficial effect of BCAA. In the BCAA group 176/239 (73%) patients survived versus 143/222 (64%) in the control group. This difference appeared to be significant using the fixed effect model (RR 1.14, 95% CI 1.01 to 1.28, P = 0.03) but did not reach statistical significance when a random effects model was applied (RR 1.11, 95% CI 0.97 to 1.26, P = 0.13). The worst-case analysis showed no significant effect of BCAA.

- Other sensitivity analyses

The effect of BCAA was not associated with the dose or duration of the BCAA intervention, the use of isonitrogenous or non-nitrogenous control, or the amount of glucose/dextrose infused. Individual patient data could not be obtained on patients with mild to moderate (stage I or II) and severe (stage III or IV) hepatic encephalopathy or to the presence or absence of iatrogenic hepatic encephalopathy (e.g., porto-systemic shunting).

Funnel plot asymmetry

There was significant funnel plot asymmetry assessed by the Begg and Mazumdar test (P = 0.048), but only a trend using the Egger et al regression test (intercept 2.82, 95% CI -0.34 to 6.00; P = 0.07).

DISCUSSION

We did not find convincing evidence that BCAA had a significant beneficial effect on patients with hepatic encephalopathy with regard to improvement of hepatic encephalopathy or survival. Although our primary analysis showed a significant beneficial effect of BCAA on the number of patients improving from hepatic encephalopathy, there was significant statistical heterogeneity and the result was not robust to sensitivity analyses. Our result may reflect bias due to low methodological quality, which was a significant source of heterogeneity. BCAA had no significant beneficial effect on hepatic encephalopathy when trials with adequate generation of the allocation sequence, adequate allocation concealment, or adequate double-blinding were analysed. Compared to these trials, the trials with low methodological quality showed a larger and significant beneficial effect of BCAA. Our results concur with empirical evidence showing that trials with low methodological quality find significantly larger beneficial treatment effects compared to trials with high methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001). This

difference in treatment effect according to methodological quality is also a likely explanation of the asymmetry seen in our funnel plot analyses (Begg 1994; Egger 1997). However, funnel plot asymmetry can reflect other biases including publication bias or the 'small study effect' (the tendency for the smaller studies in a meta-analysis to show larger treatment effects). In our case, the funnel plot asymmetry should be interpreted with caution because the included trials were small and of similar sizes (Sterne 2001).

Although it may be discussed, we chose to aggregate results from all trials assessing BCAA for hepatic encephalopathy due to the following reasons. First, both acute and chronic hepatic encephalopathy refers to a neuropsychiatric syndrome complicating hepatic failure. Aggregating all trials within the field enables us to assess the consistency and robustness of the effect of BCAA and explore potential causes for heterogeneity. The generalisability and usefulness of meta-analyses may be increased if the individual trials cover different patient populations, settings, and concomitant routine care (Gøtzsche 2000). Second, the division of hepatic encephalopathy into three categories is arbitrary. There is a sliding transition from minimal to apparent chronic encephalopathy and from chronic to acute hepatic encephalopathy where precipitating factors are considered of major importance, but are often not identified. Third, a previous systematic review on benzodiazepine receptor antagonists for hepatic encephalopathy found that seven of 12 trials included patients with either acute or chronic hepatic encephalopathy and made no differentiation between these two patient categories (Als-Nielsen 2001).

Our analyses suggested that BCAA may have a more favourable effect when given enterally to patients with chronic hepatic encephalopathy, then given parenterally to patients with acute hepatic encephalopathy. However, the amount of data on enteral BCAA to patients with chronic hepatic encephalopathy was too sparse to determine if this difference in treatment effect was reliable. We were not able to determine if this difference was due to the type of encephalopathy or the mode of administration of BCAA. Further, this analysis was based on all trials, including the trials with low methodological quality. Finally, this subgroup analysis can only be considered as hypothesis generating. Regarding minimal hepatic encephalopathy, we found a negative effect of BCAA when improvement was assessed by the number connection test (Reitan 1958), but this might be due to skewed pre-treatment values favouring the control group.

We used a random effects model because of expected clinical diversity among the included trials. In order to assess the robustness of our results we also performed the analyses using a fixed effect model. These approaches lead to some discrepancies. The discrepancies were not only due to the different models but also relates to the use of risk ratio and beneficial outcomes (improvement and survival) in our analyses (Deeks 2002). In two analyses we found discrepancies between the random and fixed effects model, with the random effects model making the results non-significant. This would not have happened if we had chosen to use the odds ratio as the summary statistic. This is because risk ratio deviates from odds ratio when the events in the control group are frequent. Our results represent one aspect in the debate regarding the selection of the appropriate summary statistic.

We found no significant association between the dose or duration and the effect of BCAA. However, it was not the aim of this review to study dose-response relationships or the effect of different treatment duration, which are examined more reliably in trials where patients are randomised to different doses or different treatment duration.

A possible cause for the observed heterogeneity could be the control or concomitant therapies. There are limits to the exploration of this heterogeneity. The concomitant therapies could not be viewed alone, because they were merged into the BCAA interventions and the different control interventions. We assessed if there was a difference in the treatment response if BCAA were assessed against isonitrogenous control or non-nitrogenous control. These control regimens were not associated with heterogeneity and there was no difference in treatment response between these two groups. The use of large infusions of glucose could be harmful, but may be negated in the experimental group because BCAA are potent secretagogues for insulin (Koretz 1990). However, the infusion of large amounts of glucose/dextrose was not associated with heterogeneity and there was no statistically significant difference in treatment response between the groups stratified according to the median amount of glucose/dextrose.

There was a considerable heterogeneity in how 'improvement' was defined and assessed in the included trials. In some trials, improvement was defined as recovery to grade 0, others to grade 0 to 1, or as regression of hepatic encephalopathy by one or two stages. In several trials, the definition of 'improvement' was not reported. Furthermore, hepatic encephalopathy was assessed using at least six different scoring systems. This heterogeneity reflects a general and unsettled problem within the field of hepatic encephalopathy. The scales and items used for defining and assessing hepatic encephalopathy are arbitrary and not tested for reliability or validity. There is a substantial need for clear diagnostic criteria of hepatic encephalopathy, as well as a reassessment and validation of scales and items used for measuring the course of the disease. A step in this direction has been the recently published consensus statement regarding hepatic encephalopathy on new terminology, definition, and diagnostic criteria (Ferenci 2002).

REVIEWERS' CONCLUSIONS

Implications for practice

We did not find convincing evidence that BCAA had a significant beneficial effect on patients with hepatic

encephalopathy. The trials performed in this field were small with short follow-up and most had low methodological quality.

Implications for research

The absence of evidence for an effect of BCAA does not mean that there is evidence of lack of effect. We believe that further randomised trials using sound research design and methodology are justified. Such trials could randomise patients with the various forms of hepatic encephalopathy (minimal hepatic encephalopathy, acute and chronic overt hepatic encephalopathy, fulminant hepatic failure) to BCAA versus placebo. All trials should use a parallel group design, due to the spontaneously fluctuating nature of hepatic encephalopathy and the need for assessing outcomes (improvement, recovery, mortality, and adverse events) after the end of treatment, e.g. after six months. All trials should be reported according to recommended guidelines (www.consort-statement.org).

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POTENTIAL CONFLICT OF INTEREST

The authors have no affiliations or financial contracts with companies producing branched-chain amino acids. Christian Gluud has been involved in a randomised clinical trial on the topic partly sponsored by Pfrimmer & Co, Germany, and Otto Broe Ltd., Denmark.

NOTES

The protocol for this review was prepared by reviewers as follows: Gluud C, Koretz R. However, the team was expanded and now the order of the reviewers of the review is as follows: Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C.

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SYNOPSIS

No convincing evidence that branched-chain amino acids have a beneficial effect on patients with hepatic encephalopathy was identified

Hepatic encephalopathy occurs in patients with chronic liver disease or fulminant liver failure and is associated with changes in mental state, ranging from minor signs of altered brain function to deep coma. Treatment with branched-chain amino acids has been proposed to ameliorate the symptoms. When all the identified trials were combined, branched-chain amino acids appeared to have a modest effect in improving encephalopathy. However, this effect was not seen when only trials of high quality were included. Thus, this review did not provide convincing evidence to support the use of branched-chain amino acids for patients with hepatic encephalopathy.

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** Indicates the major publication for the study*

Characteristics of included studies

Study	Cerra 1985 - AHE
Methods	Generation of the allocation sequence: adequate, the patients were randomised according to a computer-generated randomisation table. Allocation concealment: adequate, the computer-generated randomisation table was known only to the central pharmacy, which drew an envelope containing the treatment group and then prepared the appropriate solution. Double blinding: adequate, using placebo tablets matching the appearance of neomycin and the solutions were prepared in a double blind manner by the central pharmacy. Follow-up: inadequate (see notes).Intention to treat analyses: no. Sample size estimation: no.
Participants	75 patients with alcoholic cirrhosis (86 % males), mean age 53 years, with acute HE grade II or more that had persisted at least 48 hours before randomisation despite standard medical therapy. Precipitating factors were reported to be the same in both intervention groups and included infection, GI-bleeding, and prior surgery. Exclusion criteria: Acute viral hepatitis. Hepatorenal syndrome. Significant gastrointestinal bleeding. Acute fulminant hepatitis. Nonhepatic coma. Need for severe fluid restriction. Number of patients excluded was not reported.
Interventions	Interventions were administered daily for 14 days. Experimental: intravenous BCAA-enriched, AAA-depleted solution (F080, containing 36% BCAA) and infusion with increasing amount of 25% glucose (1.5 - 3 litre/day). Placebo tablet matching the appearance of neomycin. Total amount of received amino acids: 1 gram/kg/day. Control: intravenous 25% glucose according to similar regimen and neomycin tablets, one gram four times daily. Additional therapy was allowed to both intervention arms if clinically indicated except sedatives, lactulose, or levodopa.
Outcomes	Clinical grading of HE according to the Adam-Foley criteria. Recovery to grade 0. EEG grading. BCAA/AAA plasma molar ratio. Nitrogen balance. Mortality. Clinical grading of the encephalopathy and nitrogen balance was assessed daily. EEG grading and plasma amino acid pattern were assessed on days 0, 2, 4, 6, and 10.
Notes	Trial characteristic: crossover trial. If there was no improvement of the encephalopathy at day four, patients were crossed over to the other treatment. 16% of the patients were crossed over. Data from the first treatment period were used. Follow-up: Patients were followed for at least seven days after treatment or until death, or discharge. Only 10/40 (25%) of the patients randomised to the BCAA group completed the 14 days of treatment. Further, the data on improvement of or recovery from HE at day 14 are given for only 18 patients. Number of patients with missing data: 16 patients dropped out of the study (10 in the BCAA group, 6 in the control group). 15 of these patients died (9 in the BCAA group, 6 in the control group).
Allocation concealment	D

Characteristics of included studies

Study	Egberts 1986 - MHE
Methods	Generation of the allocation sequence: unclear (not reported). Allocation concealment: unclear (not reported). Double blinding: adequate, using identical placebo with similar taste. Follow-up: not reported. Intention to treat analyses: no. Sample size estimation: no.
Participants	22 patients with cirrhosis (73 % males), subclinical HE, and impaired driving fitness assessed by psychometric testing were included. Mean age was 52 years. 86 % had alcoholic cirrhosis and 14 % post hepatic cirrhosis. Exclusion criteria and number of patients excluded was not reported.
Interventions	Interventions were administered daily for 7 days. Patients were crossed over after end of treatment. Experimental: 0.25 g/kg BCAA per day orally + normal hospital diet providing 1 g of protein/kg/day. Control: 0.25 g casein per day orally + normal hospital diet providing 1 g of protein/kg/day. Additional treatment: Lactulose, neomycin, and psychoactive agents were individually standardized during the prestudy period and held constant throughout the study.
Outcomes	Psychometric testing. EEG grading according to Laidlaw 1963. Amino acid concentrations. Blood ammonia. Nitrogen balance. Outcomes were assessed before treatment and on the last day of each treatment period.
Notes	Trial characteristic: crossover trial. Data from the first treatment period were used. Follow-up: 4 weeks after end of treatment. Number of patients with missing data: none.
Allocation concealment	D

Study	Fiaccadori 1984- AHE
Methods	Generation of the allocation sequence: unclear (not reported). Allocation concealment: unclear (not reported). Double blinding: unclear (not reported). Follow-up: not reported. Intention to treat analyses: no. Sample size estimation: no.
Participants	48 cirrhotic patients (73 % males), mean age 51 years, with overt acute or chronic HE grade II (46 %), III (21 %), or IV (33 %). Duration of HE before randomisation was not reported. 52% had alcoholic cirrhosis, 38 % cryptogenic cirrhosis, and 32 % postnecrotic cirrhosis. Precipitating factors of HE: unknown (40 %), dehydration (23 %), GI tract bleeding (17 %), sepsis (5 %), and protein overload (5 %). Exclusion criteria: signs of hepato-renal syndrome. Number of patients excluded was not reported.

Characteristics of included studies

Interventions	Interventions were administered daily for seven days. Experimental 1: intravenous BCAA-enriched, AAA-depleted solution (BS666) + 2 litre 30% glucose. Experimental 2: intravenous BCAA-enriched, AAA-depleted solution (BS666) + 2 litre 30% glucose + 150-300 ml lactulose. Total amount of received amino acids: approximately 0.8-1 gram/kg/day. Control: intravenous 30% glucose (2 litre) and 150-300 ml lactulose. Additional treatment: antibiotics, insulin, electrolytes, and vitamins were given as needed.
Outcomes	Clinical grading of HE by according to Conn and Liberthal, 1979. Recovery to grade 0. Asterixis. Blood ammonia. EEG grading according to Kurts et al assessed in 36 patients. Number connection test assessed in 22 patients. BCAA/AAA plasma ratio. Clinical outcomes were assessed before and on the third and seventh day of therapy.
Notes	Trial characteristic: parallel group design. Data from experimental group 1 and 2 were combined. Follow-up after treatment: not reported. Number of patients with missing data: one patient dropped out in the BCAA group.
Allocation concealment	D

Study	**Hayashi 1991- CHE**
Methods	Generation of the allocation sequence: unclear (not reported). Allocation concealment: unclear (not reported). Double blinding: unclear (not reported). Follow-up: not reported. Intention to treat analyses: only used in the analysis of adverse events. Sample size estimation: no.
Participants	67 cirrhotic patients were randomised. 65 patients were included in the outcome evaluation (68 % males), mean age not possible to calculate. All patients had overt, chronic hepatic encephalopathy grade I or II and abnormality in psychometric test (number connection test, serial sevens test) or sleeping state. Duration of hepatic encephalopathy before randomisation was not reported. 58 % had cryptogenic cirrhosis, 31 % had alcoholic cirrhosis, 9 % had posthepaticic cirrhosis, 1 % had a 'specific type' of cirrhosis. Exclusion criteria: age < 15 years, GI-bleeding, complicated hepatorenal syndrome, treatment with anticancer agents, transcatheter arterial embolization or sclero-therapy for esophagus varices, women with suspected pregnancies, and patients who were judged inappropriate by the physicians in charge.
Interventions	Interventions were administerred daily for three weeks. Experimental: 160 gram ED-H given orally or by tube feeding (Elementary Diet 600 kcal, 22.4 gram total amino acids, 11 gram BCAA) and a defined diet of 1400 kcal/day containing 40 gram protein. Total of 11 gram BCAA per day. Control: 'liver diet' containing 60 g protein and 2000 kcal. Additional therapy: Lactulose, oral antibiotics and other unspecified drugs were given according to the observation period before the trial start. Aminoleban (a BCAA-enriched amino acid preparation) and plasma albumin preparation were given if needed.

Outcomes	Neuropsychiatric state assessed by the grade of portal-systemic encephalopathy "according to Sherlock", number connection test and serial seven test. Plasma ammonium. Fisher ratio. Nutritional state. General improvement (based on psychoneurological symptoms, nutritional state, and Karnofsky's Performance Status). Safety. Usefulness (based on general improvement and safety). Psychoneurological symptoms were assessed in the observation period and on day 7, 14 and 21.
Notes	Trial characteristic: parallel group design. Follow-up after treatment: not reported. Number of patients with missing data: nine patients dropped out (two in the BCAA group, five in the control group and two with unknown group assignment).
Allocation concealment	D

Study	**Hwang 1988 - AHE**
Methods	Generation of the allocation sequence: unclear (not reported). Allocation concealment: unclear (not reported). Double blinding: unclear (not reported). Follow-up: adequate. Intention to treat analyses: yes. Sample size estimation: no.
Participants	60 episodes of acute hepatic encephalopathy, grade II (11 %), III (55 %) and IV (34 %) in 55 patients (91% males), mean age 61 years. 52 of the patients had cirrhosis and 3 patients (BCAA/control: 1/2) had fulminant hepatic failure. Duration of HE before randomisation was not reported. 65 % had posthepatic cirrhosis, 15 % alcoholic cirrhosis, and 15 % other reasons for cirrhosis. Precipitating factors of HE: GI tract bleeding (36 %) infection (20 %), constipation (9 %), dietary excess (9 %), diuretics/sedatives (9 %), and other reasons (16 %). Exclusion criteria: hepatocellular carcinoma and other malignancies. Number of patients excluded was not reported.
Interventions	Interventions were administered daily for a maximum of 5 days. Experimental: intravenous BCAA-enriched, AAA depleted solution (Aminoleban) in 10% dextrose + neomycin and lactulose. Total of 40 gram BCAA per day. Control: neomycin and lactulose, doses not specified. Low protein diet (less than 20 gram/day) was given to all patients after day 3 and intravenous nutritional support was provided by dextrose solution. The amount of dextrose was not reported. Additional treatment: not reported.
Outcomes	Clinical grading of HE according to Schenker et al. 1985. Recovery to grade 0 or I. Time to recovery. Mortality. BCAA/AAA plasma ratio. Clinical grading was performed daily.

Characteristics of included studies

Notes	Trial characteristic: parallel group design. We used patients and not episodes in the analyses. Follow-up after treatment: not reported. Number of patients with missing data: none.
Allocation concealment	D

Study	**Marchesini 1990- CHE**
Methods	Generation of the allocation sequence: unclear. Treatment was given according to a numbered sequence in random order, but the method by which the allocation sequence was generated was not reported. Allocation concealment: adequate, using numbered identical packets administered sequentially. Double blinding: adequate, using identical placebo. Follow-up: adequate. Intention to treat analyses: no. Sample size estimation: yes.
Participants	64 cirrhotic patients (80 % males), mean age 60 years, with chronic HE of at least 2 months. 56 % had alcoholic, 41 % postnecrotic, and 3 % cryptogenic cirrhosis. Inclusion criteria were: alterations in three or more parameters of the PSE index, age 30 to 70 years, body weight 60 to 80 kg, lack of recent treatment with iv. BCAA-enriched solutions, co-operative relatives. Exclusion criteria: recent alcohol intake, recent gastrointestinal hemorrhage, alfa-fetoprotein levels > 10 times normal values, creatinine >1.5 mg/dl, frequent therapy changes for recurrent ascites, acute exacerbation of encephalopathy. Number of patients excluded was not reported.
Interventions	Interventions were administered daily for 3 months. Non-responders to casein were crossed over after end of treatment. Experimental: 2.4 gram oral BCAA for every 10 kg body weight. Control: equinitrogenous/equicaloric amount of oral casein containing 22% BCAA. Both groups received: 7 gram saccharose/10 kg body weight plus moderately protein-restricted diet (0.7 to 1.0 gram/kg) and lactulose adjusted to produce 1 to 2 bowel movements per day.
Outcomes	Recovery, normal mental state. Clinical grading of HE using the PSE index according to Conn 1977. Nitrogen balance. Amino acid levels. Outcomes were assessed at entry and once every month.
Notes	Combined parallel trial and crossover trial. Only data from the parallel trial were used. Follow-up after treatment: Patients who did not improve on casein were crossed over to the other treatment. Patients who had improved continued the original treatment. Accordingly, there was no follow-up after end of treatments. Number of patients with missing data: one patient was lost to follow up in the BCAA group. Two patients in the control group died. The results of these three patients were not included in the investigators analyses.
Allocation concealment	D

Characteristics of included studies

Study	Michel 1985 - AHE
Methods	Generation of the allocation sequence: unclear (not reported). Allocation concealment: adequate, using opaque envelopes. Double blinding: unclear (not reported). Follow-up: adequate. Intention to treat analyses: yes. Sample size estimation: no.
Participants	158 patients were considered for inclusion. Duration of HE before randomisation was at least 48 hours during which 32 patients died. 56 were excluded, leaving 70 cirrhotic patients (70 % males), mean age 60 years, with acute hepatic encephalopathy (HE) grade I (36 %), II (43 %), III (21 %). 81 % had alcoholic cirrhosis, 11 % posthepatitic cirrhosis, and 7 % miscellaneous reasons to cirrhosis. Precipitating factors of HE: unknown (44 %), diuretics (16 %), GI-bleeding (16 %), and infections (24 %). Exclusion criteria: Anuria, cardiopulmonary deficiency, medically unverifiable digestive haemorrhage, or septicaemia.
Interventions	Interventions were initiated 48 hours after admission and administered daily for five days. Experimental: 36 patients received intravenous BCAA-enriched, AAA depleted solution + 500 ml 30 % glucose solution and 500 ml 20% lipid emulsion. Control: 34 patients received intravenously a conventional amino acid solution (Azonutrile) + 500 ml 30%glucose solution and 500 ml 20% lipid emulsion. Total amount of received amino acids: control/experimental: 70/82 g/day None received lactulose or neomycin. Blood transfusions and intravenous antibiotics were given if needed.
Outcomes	Clinical grading of HE according to Benhamou 1961. EEG grading. Improvement, that is disappearance of HE signs or regression of HE by one stage. Mortality. BCAA/AAA plasma ratio. Clinical grading was performed twice daily and EEG grading was performed on day 1, 3 and 5 during treatment. Mortality was assessed during treatment and one month after treatment.
Notes	Trial characteristic: parallel group design. Follow-up after treatment: 1 month. Number of patients with missing data: none.
Allocation concealment	D

Study	Plauth 1993 - MHE
Methods	Generation of the allocation sequence: inadequate (not reported). Allocation concealment: unclear (not reported). Double blinding: adequate, using placebo. Follow-up: adequate. Intention to treat analyses: no Sample size estimation: no.

Characteristics of included studies

Participants	23 cirrhotic patients (65 % males), mean age 51 years, with latent encephalopathy were randomised. Six patients dropped out and 17 patients were included in the analyses. All patients had impaired driving capacity determined by psychometric testing. Duration of HE before randomisation was not reported. 88 % had alcoholic cirrhosis and 12 % posthepatitic cirrhosis. Exclusion criteria: unstable cirrhosis (transaminase level > 100 IU/l), delirium tremens in the preceding year, GI-bleeding within the preceding 14 days, unstable drug treatment during the preceding week.
Interventions	Interventions were administered daily for 8 weeks. Patients were crossed over after end of treatment. Experimental: 0.25 g/kg BCAA per day orally + their usual diet without protein restriction. Control: Placebo tablets containing neither protein nor amino acids + their usual diet. Additional treatment: preexisting treatment was continued during both treatment periods and the dosage of lactulose was held constant throughout the study.
Outcomes	Psychometric tests. Driving capacity. Biochemical tests. Outcomes were assessed before treatment and on the last day of each treatment period.
Notes	Trial characteristic: crossover trial. Follow-up: not reported. Number of patients with missing data: none.
Allocation concealment	D

Study	**Rossi 1986 - AHE**
Methods	Generation of the allocation sequence: unclear (not reported). Allocation concealment: unclear (not reported). Double blinding: unclear (not reported). Follow-up: inadequate. Intention to treat analyses: no. Sample size estimation: no.
Participants	40 cirrhotic patients (62 % males), mean age 59 years, with acute hepatic encephalopathy (HE) grade III or IV. Duration of HE before randomisation was not reported. 56 % had cryptogenic cirrhosis, 32 % alcoholic cirrhosis, and 12 % postnecrotic cirrhosis. Precipitating factors of HE: infection (35 %), GI tract bleeding (21 %), unknown reasons (15 %) and other reasons (30 %). Exclusion criteria: hepatorenal syndrome. Number of patients excluded before randomisation was not reported.
Interventions	Interventions were administered daily for at least 4 days. Experimental: intravenous BCAA- solution (BS 692) in 2 litre 20% dextrose. Total of 57 gram BCAA per day. Control: lactulose 180-240 gram/day + 2 litre 23% dextrose intravenously. Patients were treated for at least 4 days. If they did not regain consciousness after 48 hours, both lactulose and BCAA were given. Precipitating factors were treated.

Outcomes	Clinical grading of HE according to Adams and Folwy 1954. Number of patients regaining consciousness (grade 0). Time to recovery. Mortality. BCAA/AAA plasma ratio. Clinical grading was assessed twice daily.
Notes	Trial characteristic: parallel group design. However, patients not responding after 48 hours were given both the control (lactulose) and the experimental intervention. Follow-up after treatment: maximum 6 days. Number of patients with missing data: Three patients in each group dropped out. These were not included in the investigators analyses.
Allocation concealment	D

Study	**Strauss 1986 - AHE**
Methods	Generation of the allocation sequence: adequate using a random number table. Allocation concealment: adequate, using a sealed envelope system. Double blinding: inadequate, the study was unblinded comparing tablet versus infusion. Follow-up: adequate. Intention to treat analyses: no. Sample size estimation: no.
Participants	32 episodes of acute HE, grade I (9 %), II (59 %), III (31 %) in 29 cirrhotic patients (90 % males), mean age 51 years. Duration of HE before randomisation was not reported. 75 % had alcoholic cirrhosis, 13 % posthepaticic cirrhosis and 13 % cryptogenic cirrhosis. Precipitating factors of HE: infection (41 %), constipation (16 %), GI tract bleeding (9 %), hypokalemia (19 %), diuretics (6 %), and protein overload (3 %). Exclusion criteria: if patients prior to randomisation had received specific treatment for the encephalopathy (neomycin, lactulose, or L-dopa). Number of patients excluded was not reported.
Interventions	Interventions were administered daily for at least five days. Experimental: intravenous BCAA-enriched, AAA depleted solution (F080) + hypertonic glucose according to the needs of the patient. Total amount of received amino acids: 60 gram/day. Control: Oral neomycin 6 gram/24 hours + neomycin enemas. If needed, 5% glucose was given for hydration. All patients with grade 1 or 2 received 10 gram of dietary protein per day increasing with 20 gram every second day. Additional treatment comprising antibiotics, laxatives, potassium and electrolytes were given as needed.
Outcomes	Clinical grading of HE according to Conn 1977. Recovery, not defined. Time to recovery. Mortality. The time of assessment of the clinical outcomes was not reported.
Notes	Trial characteristic: parallel group design. We used episodes and not patients in our analyses. Follow-up: not reported. Number of patients with missing data: none.
Allocation concealment	D

Characteristics of included studies

Study	Vilstrup 1990 - AHE
Methods	Generation of the allocation sequence: adequate, using computer generated random numbers. Allocation concealment: adequate, using sealed opaque envelopes. Double blinding: adequate, using identical bottles. Follow-up: adequate. Intention to treat analyses: yes. Sample size estimation: yes.
Participants	Of 77 patients randomised 12 were excluded before treatment (see notes). 65 cirrhotic patients (72 % males), mean age 56 years, with acute HE grade II (31 %), III (52 %) or IV (17 %). The median duration of HE at entry was 3 days (range 1 to 14). 91 % had alcoholic cirrhosis, and 9 % posthepatitic cirrhosis. Precipitating factors of HE were presumed in 46 patients: GI tract bleeding (32 %), infection (23 %), diuretics (11 %) and unknown (29 %). Exclusion criteria: non-hepatic encephalopathy, psychosis including drug effects, lack of central venous access, oliguria, malignancy with expected life span less than one year. Number of patients excluded before randomisation was not reported.
Interventions	Interventions were administered daily for a maximum of 16 days. Experimental: 32 patients received intravenously a BCAA-enriched, AAA-depleted solution, 12.5 ml/kg/day Control: 33 patients received intravenously 8% glucose, 12.5 ml/kg/day. In addition both groups received 12.5 ml/kg/day of 50% glucose. Total amount of mean received amino acids: experimental/control: 70/0 g/day All patients received lactulose and cimetidine. Antibiotics, diuretics, blood transfusions, and insulin were given if needed.
Outcomes	HE was classified according to the Fogarty classification. Cerebral impairment scored according to the Glasgow coma scale. "Wake-up" being grade 0 or I. Mortality. BCAA plasma level. AAA plasma level. Venous ammonia level. Nitrogen balance. Clinical grading was performed at entry and at termination of the study.
Notes	Trial characteristic: parallel group design. Follow-up after treatment: none. Number of patients with missing data: 12 patients, six in each group were excluded after randomisation but before treatment due to death, inflated Sengstaken-Blakemore tube, or blood transfusions. These patients were not included in the investigators analyses.
Allocation concealment	D

Footnotes:
BCAA: branched-chain amino acids
AAA: aromatic amino acids
HE: hepatic encephalopathy
GI: gastrointestinal
PSE index: portal-systemic encephalopathy index

Characteristics of excluded studies

Study	Reason for exclusion
Achord 1987	A randomised trial assessing the effect of an amino acid-glucose infusion in patients with acute alcoholic hepatitis. The trial is excluded because, the experimental treatment was a standard amino acid preparation and not enriched with BCAA and only 6/40 patients had hepatic encephalopathy at entry.
Baker 1987	A review article.
Bernardi 1981	A review article.
Bianchi 1993	A randomised controlled trial comparing vegetable versus animal protein diet (and not branched-chain amino acids) in cirrhotic patients with chronic hepatic encephalopathy. The trial concluded that a mainly vegetable protein diet is worthwhile in cirrhotic patients with chronic encephalopathy under optimum lactulose therapy.
Bonkovsky 1991	The randomised trial evaluated the efficacy of treatment with parenteral nutrition and/or oxandrolone in patients with alcoholic hepatitis. No data are given on hepatic encephalopathy at entry or at end of treatment or follow-up.
Bunout 1989	A randomised trial evaluating the efficacy of a casein-based nutritional supplementation in patients with alcoholic liver disease. An intervention with BCAA was not used and only 10/36 patients had hepatic encephalopathy at entry.
Caballeria 1987a	The study was quasi-randomised and excluded ("Patients were assigned in an alternate way in the order they entered the study").
Caballeria 1987b	Not a randomised trial, but an observational study.
Cabre 1990	The trial evaluated the effect of enteral nutrition in cirrhotic patients and only 4/35 had hepatic encephalopathy at entry.
Cabre 2000	A randomised trial comparing total enteral nutrition enriched in branched-chain amino acids with steroids in patients with severe alcohol-induced hepatitis. The trial is excluded because only a subgroup (28%) of the included patients had hepatic encephalopathy at entry.
Calvey 1985	Randomised trial assessing the effect of BCAA in patients with acute alcoholic hepatitis regardless of encephalopathy. Only 30/64 had hepatic encephalopathy at entry. Accordingly, the trial is excluded.
Chin 1992	A randomised trial assessing branched-chained amino acids in 19 children with end-stage liver disease. The patients included were without clinical evidence of encephalopathy and the trial is therefore excluded.
Christie 1985	A randomised crossover trial comparing an enriched branched-chain amino acid formula with a casein-based supplement in the treatment of eight patients with cirrhosis. Only 3/8 patients had hepatic encephalopathy at entry and the trial is accordingly excluded.
Cortez 1990	Randomised trial comparing parenteral nutrition with oral nutrition with similar amounts of macronutrients. Accordingly, an BCAA-intervention was not used.
Cowan 1986	A letter commenting on the results of the Cerra trial.
De Antoni 1984	Excluded, as the study was not randomised.
De Bruijn1983	Not a randomised trial, but a controlled clinical trial, evaluating the effect of animal versus vegetable protein in patients with subclinical portal-systemic encephalopathy. The different vegetable and animal diets had equal amounts of branched-chain amino acids; accordingly the study did not evaluate the effect of BCAA-enriched solutions.

Characteristics of excluded studies

De Lédinghen 1997	A randomised trial assessing the nutritional and clinical effects of early enteral nutrition (EN) in cirrhotic patients with bleeding from esophageal varices. Excluded due to not using BCAA as the experimental intervention.
Diehl 1985	A randomised trial assessing the effect of an amino acid-glucose infusion in patients with acute alcoholic hepatitis. The trial is excluded because the experimental treatment was a standard amino acid preparation and not enriched with BCAA. Further, the numbers of patients having hepatic encephalopathy at the beginning and at the end of the trial was not reported.
Dioguardi 1990	Not a randomised trial, but an open prospective study evaluating the efficacy of an oral branched-chain amino acid supplementation in 28 cirrhotic patients. The number of patients having hepatic encephalopathy at entry is not reported.
Egberts 1987	A review article of published controlled clinical trials with branched chain amino acids in patients with portosystemic encephalopathy. The review concluded that a positive effect on portosystemic encephalopathy by BCAA seems probable but without altering mortality rate.
Erikkson 1982	A double-blind quasi-randomised trial assessing the effect of oral BCAA in patients with chronic hepatic encephalopathy. The trial found no significant difference in clinical improvement between the two groups.
Eriksson 1984	A review article.
Ferenci 1981	A crossover study evaluating the effect of orally administered BCAA and branched chain keto acids in patients with chronic hepatic encephalopathy. The study is not described as randomised.
Fiaccadori 1988	A randomised trial including ten cirrhotic patients with chronic recurrent encephalopathy. At the time of inclusion the patients had either no or grade 1 hepatic encephalopathy. The trial reports that " encephalopathy did not develop during the observation period". Accordingly, the trial is a prevention trial and excluded.
Fischer 1984b	A review article.
Greenberger 1977	A single blind, randomised, crossover trial comprising three patients and comparing the efficacy of a vegetable diet versus animal diets. The trial did not use a BCAA or a BCAA-enriched intervention.
Grungreiff 1993	The study is a randomised trial comparing the effect of a BCAA-enriched solution with an BCAA-enriched solution + extra L-valine. The trial is excluded because, according to our protocol, we only include trials comparing BCAA with no nutritional support, placebo support, isocaloric support, or isonitrogenous support.
Hartung 1989	A letter referring to a trial evaluating the effect of infusion with ornithine aspartate on plasma ammonia and plasma amino acids in patients with cirrhosis. Ornithine aspartate is not a branched-chain amino acid.
Hasse 1995	Randomised trial assessing the effects of early postoperative tube feeding on different outcomes of liver transplant recipients. The trial is excluded because the patients did not have hepatic encephalopathy at entry and hepatic encephalopathy was not considered an outcome.
Hertelendy 1993	A randomised controlled trial evaluating the clinical and biochemical effects of aspartame (an artificial sweetener which is composed of 50 % phenylalanine, an aromatic amino acid). The trial does not evaluate the effect of a branched-chain amino acid treatment. The trial concludes that patients with chronic, stable liver disease can safely use aspartame.

Characteristics of excluded studies

Higuchi 1994	Not a randomised controlled trial, but a historically controlled study comprising six cirrhotic patients with mild encephalopathy (grade I and II) and five control patients selected from inpatients with non-hepatic disorders. A branched-chain-enriched amino acid solution was infused and neurophysiological changes and psychometric tests were evaluated. The study concluded that branched-chain amino acids functioned as psychotropic drug for cirrhotic patients with mild hepatic encephalopathy.
Hirsch 1993	Randomised clinical trial assessing the effect of an oral casein supplementation given over a year to ambulatory patients with decompensated alcoholic liver disease. The trial is excluded due to not using a BCAA intervention.
Holm 1979	A study comparing three different BCAA solutions in 120 cirrhotic patients. The study is not randomised nor described as blinded. Further, only a subgroup of the included patients had hepatic encephalopathy at entry. Part of the study is reported in the Striebel study 1979.
Holm 1991	Randomised trial comparing ornithine aspartate with placebo on blood amino acid patterns in cirrhotic patients. The trial is excluded because the patients did not have hepatic encephalopathy at entry and no outcomes concerning grade of HE are mentioned and it did not evaluate BCAA.
Horst 1984	Randomised trial assessing the encephalopathy-inducing capacity of BCAA by comparing dietary protein with BCAA in protein-intolerant cirrhotic patients. At entry patients had either normal mental state or stable grade 1 encephalopathy and the goal of the trial was not to assess BCAA in the treatment of hepatic encephalopathy, but to assess if BCAA induced encephalopathy less frequently than dietary protein.
Ichida 1995	Not a randomised controlled trial, but a historically controlled study. 96 patients with decompensated liver cirrhosis and grade II hepatic coma or a history of hepatic encephalopathy were included in the study. 72 patients were treated with an enteral branched-chain amino acid solution. The survival rates for the treated patients were compared with control patients being treated for decompensated liver cirrhosis during the preceding five years in the participating hospitals.
Kanematsu 1988	A randomised trial evaluating the preventive effect of BCAA in postoperative liver patients. The patients participating did not have hepatic encephalopathy at entry, why this study is excluded.
Kearns 1992	Randomised controlled trial comparing casein-based tube-fed supplement with regular diet in patients with alcoholic liver disease. 17/31 patients had hepatic encephalopathy at entry. Excluded because the trial did not use a BCAA-intervention.
Keohane 1983	Observational study assessing the effect of BCAA in 10 cirrhotic patients with hepatic encephalopathy grade I to III.
Ker 1986	Not a randomised, controlled trial, but an observational study comprising 19 case series.
Keshavarzian 1984	A randomised trial comparing a conventional protein diet with a vegetable-protein-supplemented diet in patients with chronic stable portal systemic encephalopathy. The trial concluded that patients with chronic portal systemic encephalopathy are tolerant of protein supplementation from vegetable sources. The trial did not evaluate an intervention with BCAA.
Kircheis 1997	A randomised trial assessing the efficacy of treatment with L-ornithine-L-aspartate infusions in patients with hepatic encephalopathy. The trial is excluded due to not using BCAA as the experimental intervention regimen.
Langhans 1981	Not a randomised trial, but a controlled study assessing the effect of different amounts of dietary protein +/- BCAA supplementation in four groups of patients with liver cirrhosis and latent hepatic encephalopathy.

Characteristics of excluded studies

Leweling 1980	Not a randomised trial, but an uncontrolled study comprising 10 patients with cirrhosis who were divided in two groups: In group A (5 patients) none of the patients had hepatic encephalopathy as opposed to group B (5 patients) where all of the patients had hepatic encephalopathy. The plasma amino acid pattern was measured in both groups before and after BCAA administration. In group B there were 11 episodes of hepatic encephalopathy, the degree of which was measured before and after BCAA administration.
Leweling 1990	The trial is a metabolic study, assessing the effects of ornithine aspartate on plasma ammonia and plasma amino acids. The trial did not evaulate a BCAA intervention.
Marchesini 1980	A historically controlled trial, using normal subjects as baseline control.
Marchesini 1987	A metabolic study evaluating the plasma clearances of branched-chain amino acids in cirrhotic patients and control subjects. Not a randomised trial.
Marchini 1983	Randomised clinical trial assessing the plasma amino acid pattern and nitrogen balance in chronic alcoholics fed with two different energy sources. The 20 patients were divided in three groups, and the three groups received similar amounts of essential amino acids. The amino acid solution was not enriched with BCAA.
McCullough 1981	A controlled trial comparing serum amino acid levels in 29 patients with severe chronic active liver disease before, during, and after administration of prednisone or placebo and in 22 healthy controls. No intervention regime with BCAA was used.
Mendenhall 1985	Excluded due to not being a randomised trial, but a historical controlled study.
Mendenhall 1993	A randomised trial assessing the effect of a combination therapy consisting of oxandrolone and BCAA-enriched supplement compared to low-calorie, low-protein food supplement and placebo tablets. Standard therapy for any complicating conditions (e.g. encephalopathy) was provided. The trial is excluded because only a subgroup (64%) of the patients had hepatic encephalopathy at entry and because BCAA therapy was not assessed as a treatment for hepatic encephalopathy.
Meng 1999	A randomised trial evaluating the effect of branched-chain amino acids in patients undergoing liver resection. None of the patients had hepatic encephalopathy at entry.
Messner 1982	A randomised, double-blind trial evaluating lactulose versus bromocriptine on the plasma ratio BCAA/AAA. The trial did not evaluate a BCAA intervention.
Mezey 1991	A randomised trial evaluating the effect of parenteral amino acid supplementation - not a BCAA-enriched solution - in patients with severe alcoholic hepatitis. Among the 54 included patients, 10 had hepatic encephalopathy at entry. Hepatic encephalopathy was not considered as an outcome.
Michel 1985	The trial assessed the effect of exclusive parenteral nutrition in patients with alcoholic cirrhosis. The patients did not have hepatic encephalopathy at entry and none of the patients developed hepatic encephalopathy during the trial. Further the trial was not randomised, nor was the intervention described as BCAA-therapy.
Millikan 1983	Not a randomised trial, but seven case-series in three patients with subclinical encephalopathy given an increasing amount of BCAA-enriched solution. The study did not find a significant change in encephalopathy from baseline.
Mital 1967	A cohort study describing 72 patients with hepatic encephalopathy. No intervention was tested.
Montanari 1988	Not a randomised trial, but a controlled clinical study evaluating the effect of oral administration of BCAA on amino acids in plasma and intracellular water. The included patients had liver cirrhosis and not hepatic encephalopathy.

Characteristics of excluded studies

Montet 2000	Randomised clinical trial assessing the effect of L-arginine treatment in preventing hepatic encephalopathy. Excluded due to not using a BCAA as the experimental intervention. Further, the included patients did not have hepatic encephalopathy at entry.
Morioka 1983	Not a randomised trial, but a controlled study assessing the effect of intravenous infusion of BCAA solution on blood glucose, insulin, and glucagon levels of cirrhotic patients and normal volunteer subjects.
Muto 1984	A crossover study comprising eight patients, out of whom one patient had encephalopathy. The patients received BCAA for four weeks after which they were crossed over to placebo or vice versa. The evaluated outcomes were changes in plasma amino acid levels, blood ammonia levels, nitrogen balance, and serum albumin concentration.
Muto 1991	A randomised trial comparing the effect of BCAA with placebo given to patients with liver cirrhosis. The patients did not have hepatic encephalopathy at entry and this was not assessed as an outcome. Accordingly, the trial was excluded.
Nasrallah 1980	Randomised trial comprising 35 patients with alcoholic hepatitis. Only eight of the patients had hepatic encephalopathy at entry, and the intervention assessed was not a BCAA treatment but a standard amino acid solution (P-900). Accordingly, the trial was excluded.
Naveau 1986	The included patients were not all encephalopathic (only 7/40). The intervention that was used was not BCCA-enriched solution, but an oral diet containing 40 kcal per kg/day compared to oral diet + a supplementary parenteral nutrition. Both the participants and the interventions used did not match the focus of this review.
O'Keefe 1987	A randomised trial comprising eight patients with alcoholic liver failure. Four patients were randomised to intravenous diet with a total amount of amino acids 60-80 g/day, BCAA content 51% versus four patients given enteral treatment with a diet containing a total of 58 g amino acids, BCAA content 43%. According to our protocol we only include trials comparing BCAA with no nutritional support, placebo support, isocaloric support, or isonitrogenous support.
Okita 1985	Not a randomised trial, but a time-series study. Ten patients were first treated with a control diet during which basal data were collected. Thereafter, the patients were treated with BCAA-enriched nutrient mixture and a comparison was made between the two periods.
Okuno 1985	The study evaluates three postoperative parenteral nutritional regimens in 61 patients with liver disorders. The patients did not have hepatic encephalopathy. The study is not described as randomised. The study evaluates laboratory tests, serum amino acid patterns, and body weight changes in the groups of patients receiving the different nutritional regimens.
Pachl 1988	A controlled trial, but not randomised. A total of 51 children participated in the study. Group A (23 patients) received conventional amino acid solution combined with a glucose solution. Group B received in addition a BCAA solution.
Pesendorfer 1980	An observational study assessing the effect of treatment with ornithine-alpha-ketoglutarate in patients with hepatic encephalopathy. The study is excluded due to not being randomised and not using BCAA as the experimental intervention.
Puglionisi 1984	The study examines the effectiveness of BCAA solutions in the prevention of hepatic encephalopathy after porta-caval anastomosis. The patients did not have hepatic encephalopathy at entry. Two patients (out of 10) in the control group develop hepatic encephalopathy after surgery. None of the patients in the BCAA group develops hepatic encephalopathy.
Qian 1986	Not a randomised trial, but an observational study comprising 17 patients with chronic hepatic encephalopathy and 35 patients with chronic hepatitis. Both groups received oral BCAA treatment.

Characteristics of excluded studies

Rakette 1981	Controlled study including 37 patients with various degrees of hepatic encephalopathy (including some not having hepatic encephalopathy). Patients were allocated to three groups receiving BCAA, BCAA + low amount of aromatic amino acids, glucose. The study is not described as randomised and accordingly excluded.
Reilly 1990	Randomised trial comparing BCAA-therapy, standard total parenteral nutrition, and placebo in 28 liver transplanted patients of whom 10 had hepatic encephalopathy at entry. The patients entered the study immediately before or after liver transplantation. Accordingly, the course of hepatic encephalopathy must be regarded as due to the transplantation. The trial reported that within 24 to 36 hours after transplantation, all patients were alert. There were no differences with regard to hepatic encephalopathy between the three groups.
Riederer 1980	The trial is excluded due to being a historically controlled study comparing concentrations of amino acids in the brain of patients treated with L-valine + parenteral nutrition with historically control subjects.
Riggio 1984	Randomised trial assessing the preventive effect of BCAA in 28 patients with chronic recurrent hepatic encephalopathy. The patients did not have hepatic encephalopathy at entry.
Rocchi 1984	A randomised trial, evaluating the effect of BCAA infusion compared to standard amino acids solution on plasma amino acid pattern in 22 cirrhotic patients without encephalopathy. Thus the patients included did not have hepatic encephalopathy at entry and this was not evaluated as an outcome.
Rocchi 1985	A randomised trial comprising 36 cirrhotic patients without encephalopathy evaluating the effect of BCCA-enriched solution versus standard amino acid mixtures on nutritional parameters.
San-In Group 1997	A randomised clinical trial assessing the effect of long-term oral administration of BCAA in patients undergoing hepatic resection for primary hepatocellular carcinoma. The trial is excluded because no patients had encephalopathy at the time of entry. During the follow-up, several patients had encephalopathy of slight degree, the incidence of which was relatively lower in the BCAA-treated group.
Schäfer 1981	A controlled study including eight patients who in alternate time periods received different protein mixtures (including a BCAA-enriched mixture) or an isocaloric carbohydrate mixture. The study is excluded due to not being randomised.
Shaw 1983	The trial is excluded due to not being randomised and not using BCAA as the experimental intervention. The study compared animal protein with vegetable protein in the management of hepatic encephalopathy.
Sieg 1983	Randomised crossover trial assessing BCAA therapy in 14 patients with cirrhosis. Only a subgroup of the patients had hepatic encephalopathy at entry and accordingly the trial did not assess BCAA for the treatment of hepatic encephalopathy but assessed whether BCAA as a nitrogen source were well tolerated by the cirrhotic patients.
Sievert 1999	A randomised trial with three intervention arms comparing 1) enteral supplements enriched with BCAA (45%) with 2) enteral supplements containing 20% BCAA and 3) placebo. The included patients had liver cirrhosis and were malnourished. There was no data regarding the number of patients having hepatic encephalopathy at entry and this was not an inclusion criteria. Accordingly, the trial was excluded.
Silk 1986	A review article.
Simko 1983	Randomised trial assessing BCAA therapy in 15 patients with a history of previous hepatic encephalopathy. The patients were given increasing amount of BCAA to assess the tolerance of BCAA therapy. Accordingly, the trial was excluded.

Characteristics of excluded studies

Simon 1988	Randomised trial assessing parenteral nutrition in 34 patients with alcoholic hepatitis. Only few of the included patients had hepatic encephalopathy at entry and the intervention was not given as a treatment for hepatic encephalopathy, but as a treatment of alcoholic hepatitis.
Swart 1981	Controlled study comparing BCAA-enriched diet with natural protein diet in eight cirrhotic patients with previous encephalopathy. At entry the patients did not have hepatic encephalopathy and it did not occur during the study. Furthermore, the trial is not described as randomised ("natural and BCAA enriched protein were given alternatingly").
Tangkijvanich 2000	A randomized study including 29 ambulatory cirrhotic patients to determine the short-term effects of BCAA on nutritional status, biochemical liver function tests and caffeine clearance. Hepatic encephalopathy was not used as an inclusion criterion, nor assessed as an outcome.
Uribe 1982	A randomised, single-blind, crossover trial comparing standard diet therapy (40 g/day meat protein diet plus neomycin-milk of magnesia) versus a 40 g/day vegetable protein diet or an 80 g/day vegetable protein diet in 10 cirrhotic patients with mild chronic portal-systemic encephalopathy. The mean molar BCAA/AAA ratio was respectively 3.60/3.60/3.48. The trial did not use a BCAA /or BCAA-enriched solution in one of the interventions arms.
Uribe 1985	A randomised trial evaluating the effect of a vegetable protein diet supplemented with psyllium plantago versus a meat protein diet. The trial proposed the use of vegetable diet plus fibre to facilitate the treatment of patients with both diabetes and hepatic encephalopathy. The trial did not evaluate an intervention with BCAA.
Wahren 1983	A double-blind quasi-randomised trial assessing the effect of intravenous BCAA in patients with acute hepatic encephalopathy. The trial found no significant difference in clinical improvement or mortality between the two groups.
Walker 1982	A randomised, double-blind, crossover trial of keto analogs of BCAA. Keto analogs are not included in the types of interventions that we evaluate in this Review.
Walser 1981	A review article summarising the knowledge concerning the effect of branched-chain keto acids and comparing these effects with those of BCAA.
Watanabe 1983	Not a randomised trial. A BCAA-enriched product was given to six cirrhotic patients - of which only three had had a history of hepatic encephalopathy - and two healthy controls. Laboratory and psychometric parameters were measured before and after the experimental diet.
Weber 1981	A review article.
Weber 1990	Not a randomised trial. The study comprised of nine cirrhotic patients of whom six patients had had prior episodes of hepatic encephalopathy and only two patients had hepatic encephalopathy at the time of the study. The study evaluated the effect of a BCCA-enriched solution compared to a standard amino acid solution on protein catabolic rates and plasma ammonia levels. Excluded because it is not a randomised trial and because the participants do not have hepatic encephalopathy at entry.
Wicks 1994	Excluded due to not using BCAA as the experimental intervention. Further patients were not reported having hepatic encephalopathy at entry and hepatic encephalopathy was not assessed as an outcome.
Yoshida 1989	Not a randomised trial, but the article reports the findings of a prospective cohort study and a controlled, clinical trial. The latter evaluated the efficacy of long-term oral supplementation with BCAA to cirrhotic patients. The numbers of patients having hepatic encephalopathy at entry or at end of treatment are not reported.

ADDITIONAL TABLES

Table 01 Methodological quality - components

GENERATION OF THE ALLOCATION SEQUENCE	ALLOCATION CONCEALMENT	DOUBLE BLINDING
Adequate: table of random numbers, computer generated random numbers or similar.	Adequate: concealed up to the point of treatment by central randomisation, sealed envelopes or similar.	Adequate: using identical placebo or similar.
Unclear: the trial was described as randomised, but the generation of the allocation sequence was not described.	Unclear: the allocation concealment was not described.	Unclear: the trial was described as double blind, but the method of blinding was not described
Inadequate: quasi-randomised trials (excluded).	Inadequate: open table of random numbers or similar.	Inadequate: tablets versus injections or similar.

COVER SHEET

Title	**Branched-chain amino acids for hepatic encephalopathy**
Reviewer(s)	**Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C**
Contribution of reviewer(s)	Christian Gluud and Ronald Koretz wrote the original protocol, which was revised by Bodil Als-Nielsen, who performed the searches, selected trials for inclusion, wrote to authors and pharmaceutical companies, performed data extraction and data analysis, and drafted the systematic review. Ronald Koretz has performed a comprehensive handsearch covering this field through many years. Further, Ronald Koretz performed data extraction, revised the protocol, and the systematic review. Lise Lotte Kjaergard and Christian Gluud revised the protocol and the systematic review.
Issue protocol first published	1997/1
Issue review first published	2003/2
Date of most recent amendment	26 November 2002
Date of most recent SUBSTANTIVE amendment	19 September 2002

Most recent changes	**Changes to the original protocol:We have now specified that crossover trials were included in the review and that data from the first period would be used.Patients with fulminant hepatic failure were included in 'Types of participants' in order to include all patients with hepatic encephalopathy. In addition, these patients were included in the intended sensitivity analysis regarding the form of hepatic encephalopathy. In our primary protocol we wanted to assess 'Recovery'. However, there was a substantial heterogeneity in the definition of 'recovery' ranging from no definition (one trial), "recovery to grade 0-1" (two trials) to "full recovery" (three trials). The remaining five trials did not assess 'recovery' but 'improvement' of hepatic encephalopathy. In order to comply with this, we decided post hoc to assess improvement rather than recovery. The outcome measure 'improvement' includes partial and full recovery. We have changed the assessment of methodological quality according to recent empirical evidence. We have included an assessment of funnel plot asymmetry in order to assess the risk of publication bias and other biases.We have clarified the statistical analyses regarding the 'intention-to-treat' and 'worst-case-scenario' methods and included best-case-scenario analyses. We have included sensitivity analyses regarding methodological quality, control therapy, and concomitant therapy. According to the latest recommendations in he Cochrane Reviewers' Handbook, we abandoned the decision to base our choice between fixed and random effects meta-analysis on the result of a test for heterogeneity. Instead, analyses were performed based on a random effects model due to anticipated variability between trials regarding patient populations, interventions, and concomitant regimens. To assess the robustness of the results, analyses were also performed using a fixed effect model.**
Date new studies sought but none found	16 September 2002
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	16 September 2002
Date reviewers' conclusions section amended	Information not supplied by reviewer
Contact address	Dr Bodil Als-Nielsen MD The Cochrane Hepato-Biliary Group Copenhagen Trial Unit, Centre for Clinical Intervention Research Copenhagen University Hospital Department 7102, H:S Rigshospitalet Blegdamsvej 9 DK-2100 Copenhagen DENMARK Telephone: +45 3545 7161 E-mail: Bodil.a@ctu.rh.dk Facsimile: +45 3545 7101
Cochrane Library number	CD001939

Editorial group	Cochrane Hepato-Biliary Group
Editorial group code	HM-LIVER

SUMMARY TABLES

01 BCAA versus control				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Improvement at the end of treatment	9	528	Relative Risk (Random) 95% CI	1.31 [1.04, 1.66]
02 Survival at the end of treatment	8	461	Relative Risk (Random) 95% CI	1.05 [0.98, 1.12]
03 Survival at the end of maximum follow-up	8	461	Relative Risk (Random) 95% CI	1.06 [0.98, 1.14]
04 Number of patients experiencing adverse events	3	165	Relative Risk (Random) 95% CI	0.97 [0.41, 2.31]
05 Improvement (posttreatment values) assessed by the Number Connection Test			Weighted Mean Difference (Random) 95% CI	Subtotals only
06 Time to improvement	3	79	Weighted Mean Difference (Random) 95% CI	-14.08 [-37.77, 9.62]

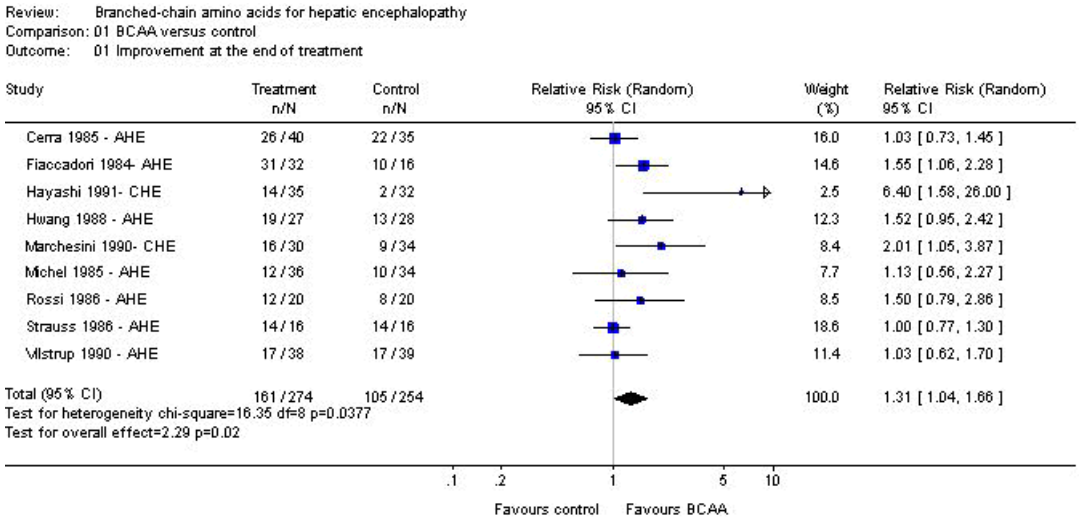
02 Sensitivity analyses - BCAA versus control (improvement)				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Methodological quality - Improvement			Relative Risk (Random) 95% CI	Subtotals only
02 Form of hepatic encephalopathy and mode of administration - Improvement	9	528	Relative Risk (Random) 95% CI	1.31 [1.04, 1.66]
03 Dose and duration of BCAA intervention - Improvement			Relative Risk (Random) 95% CI	Subtotals only
04 Isonitrogenous versus non-nitrogenous control - Improvement	9	528	Relative Risk (Random) 95% CI	1.31 [1.04, 1.66]
05 Amount of glucose/dextrose infusion - Improvement	5	310	Relative Risk (Random) 95% CI	1.21 [0.99, 1.49]
06 Worst case scenario favouring control therapy - Improvement	9	528	Relative Risk (Random) 95% CI	1.18 [0.98, 1.43]
07 Best case scenario favouring BCAA - Improvement	9	528	Relative Risk (Random) 95% CI	1.44 [1.11, 1.86]

03 Sensitivity analyses - BCAA versus control (survival)				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Methodological quality - Survival			Relative Risk (Random) 95% CI	Subtotals only
02 Form of hepatic encephalopathy and mode of administration - Survival	8	461	Relative Risk (Random) 95% CI	1.06 [0.98, 1.14]
03 Dose and duration of BCAA intervention - Survival			Relative Risk (Random) 95% CI	Subtotals only
04 Isonitrogenous versus non-nitrogenous control - Survival	8	461	Relative Risk (Random) 95% CI	1.06 [0.98, 1.14]
05 Amount of glucose/dextrose infusion - Survival	5	310	Relative Risk (Random) 95% CI	1.07 [0.88, 1.30]
06 Worst case scenario favouring control therapy - Survival at maximum follow up	8	461	Relative Risk (Random) 95% CI	1.01 [0.89, 1.14]
07 Best case scenario favouring BCAA - Survival at maximum follow up	8	461	Relative Risk (Random) 95% CI	1.11 [0.97, 1.26]

GRAPHS AND OTHER TABLES

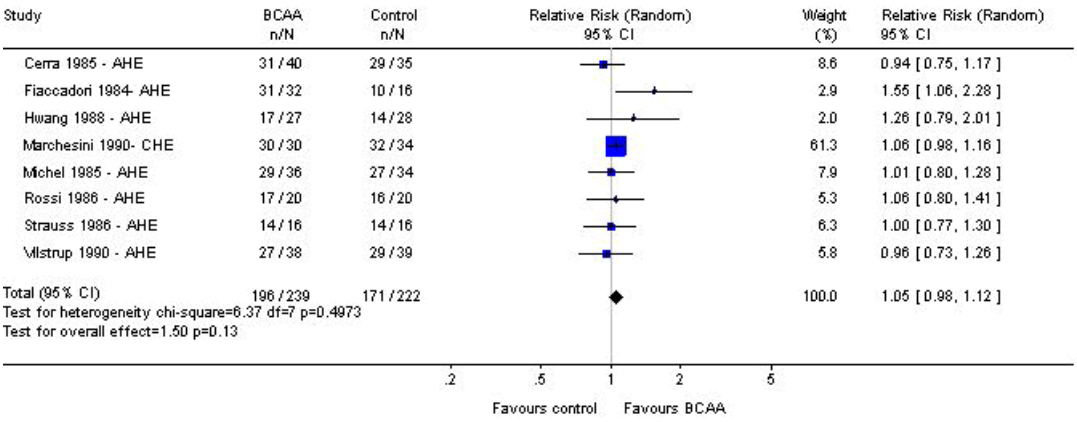
Fig. 01 BCAA versus control

01.01 Improvement at the end of treatment



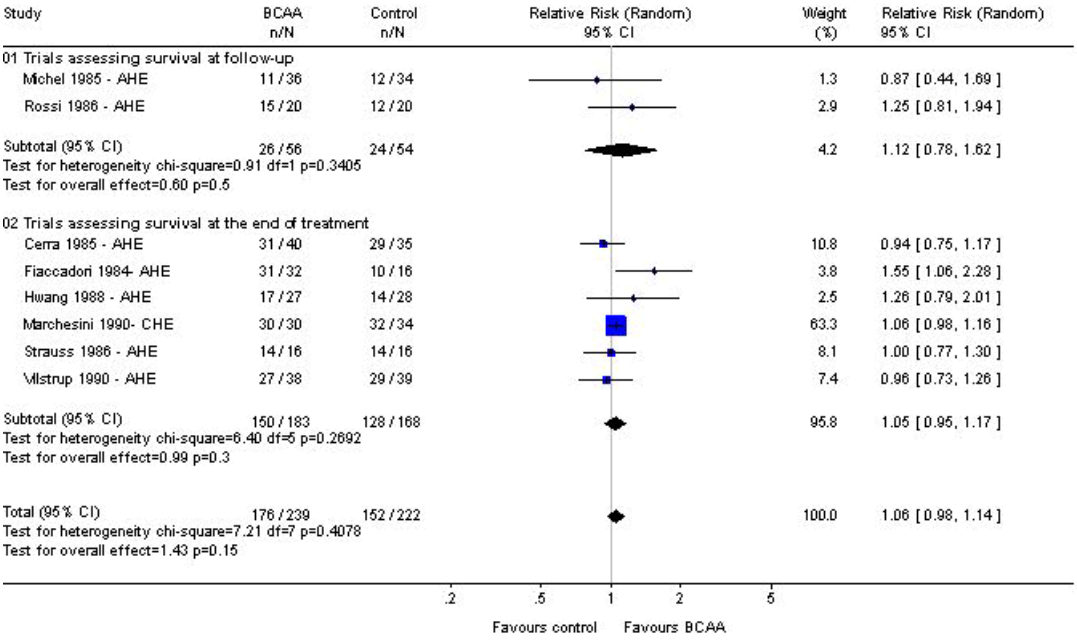
01.02 Survival at the end of treatment

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 01 BCAA versus control
Outcome: 02 Survival at the end of treatment



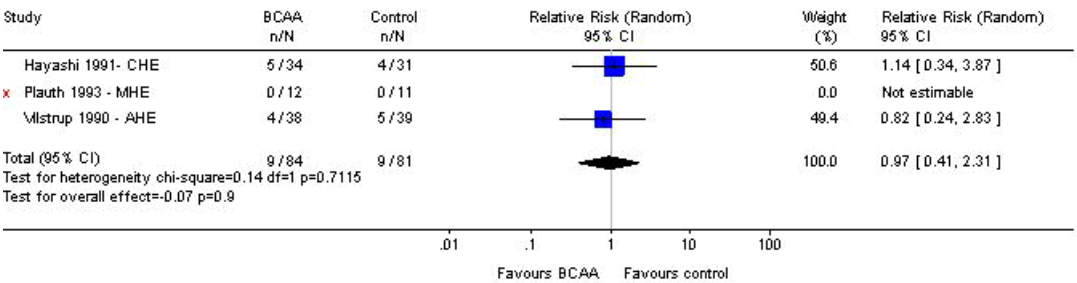
01.03 Survival at the end of maximum follow-up

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 01 BCAA versus control
Outcome: 03 Survival at the end of maximum follow-up



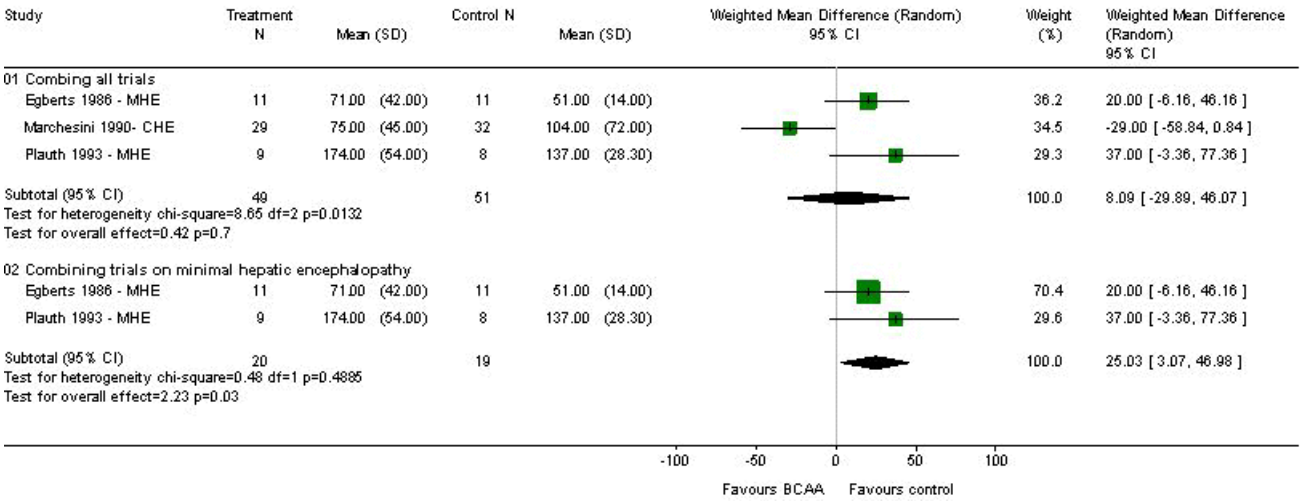
01.04 Number of patients experiencing adverse events

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 01 BCAA versus control
Outcome: 04 Number of patients experiencing adverse events



01.05 Improvement (posttreatment values) assessed by the Number Connection Test

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 01 BCAA versus control
Outcome: 05 Improvement (posttreatment values) assessed by the Number Connection Test



01.06 Time to improvement

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 01 BCAA versus control
Outcome: 06 Time to improvement

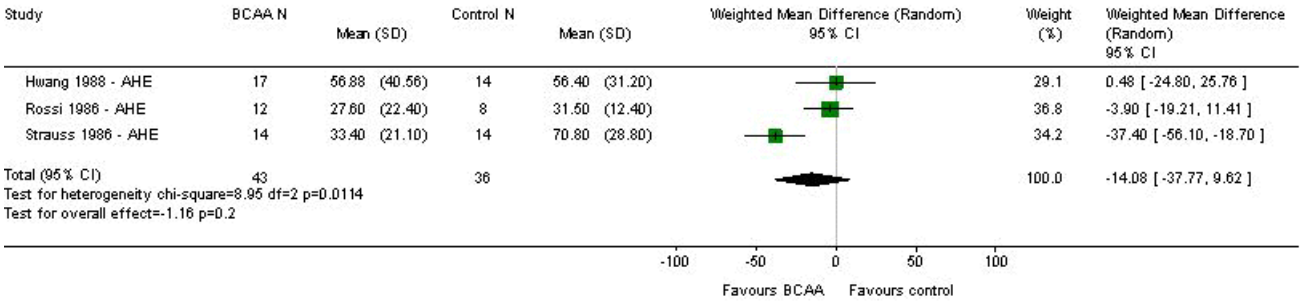
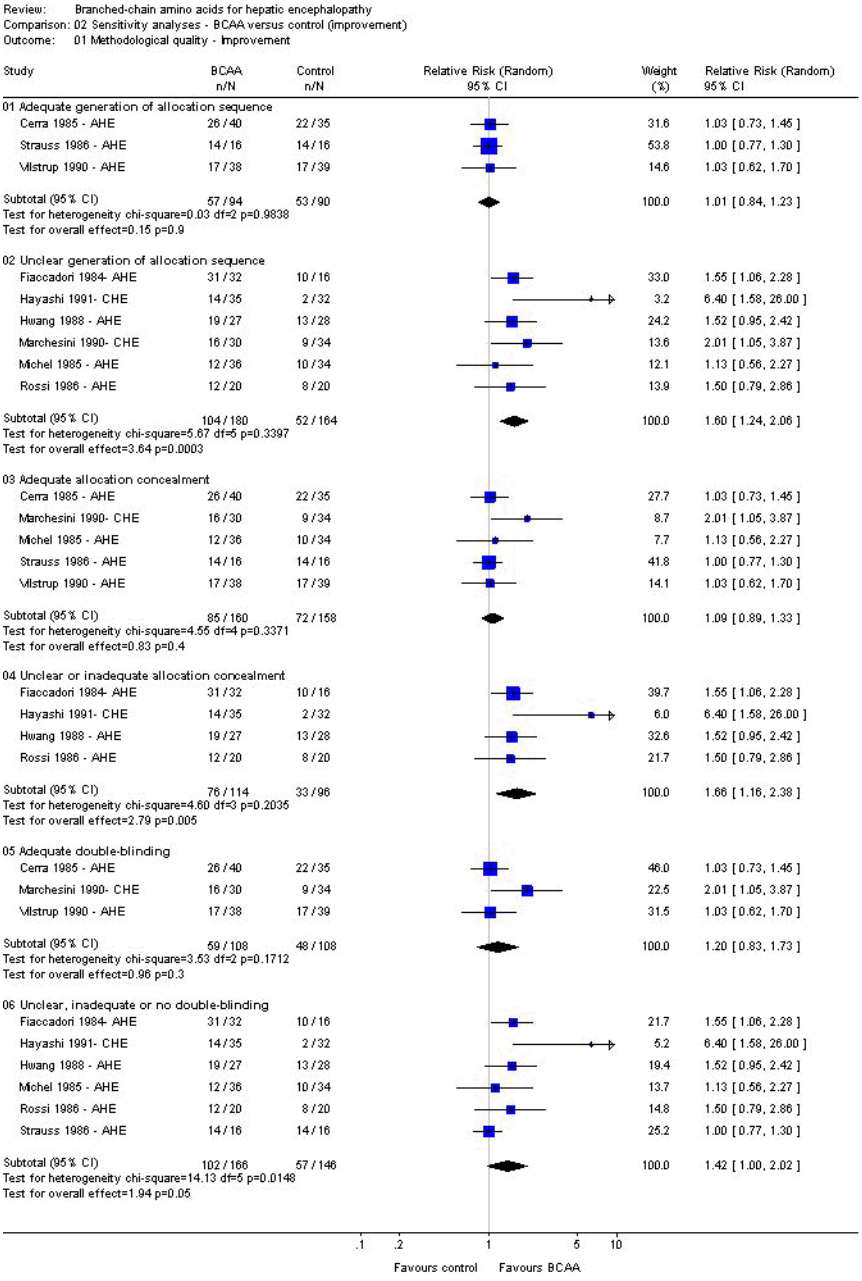


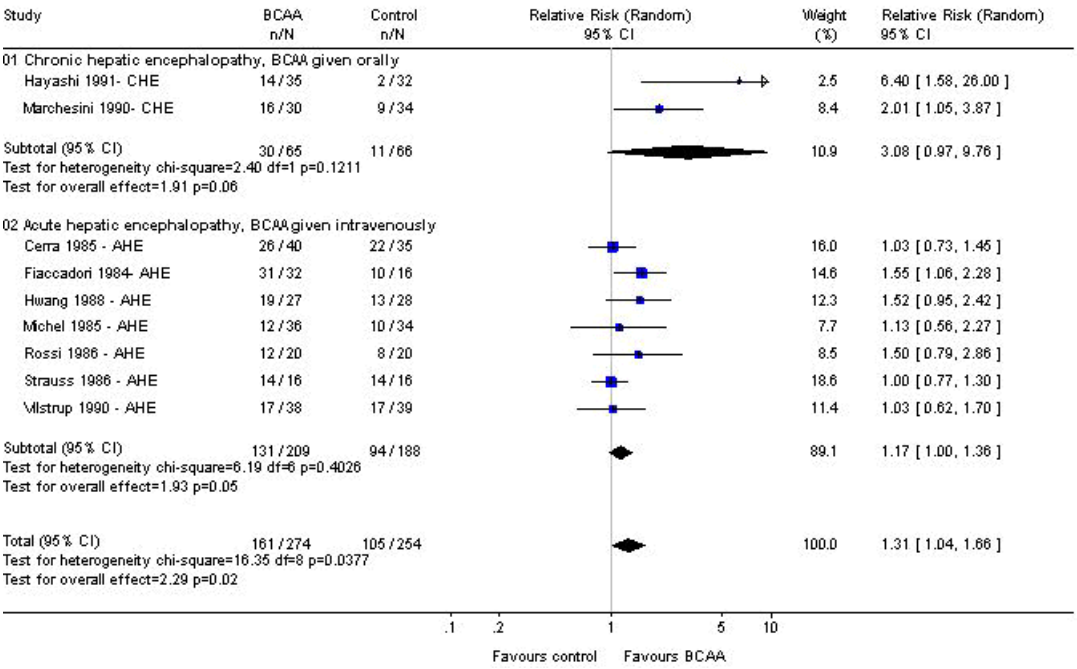
Fig. 02 Sensitivity analyses - BCAA versus control (improvement)

02.01 Methodological quality - Improvement



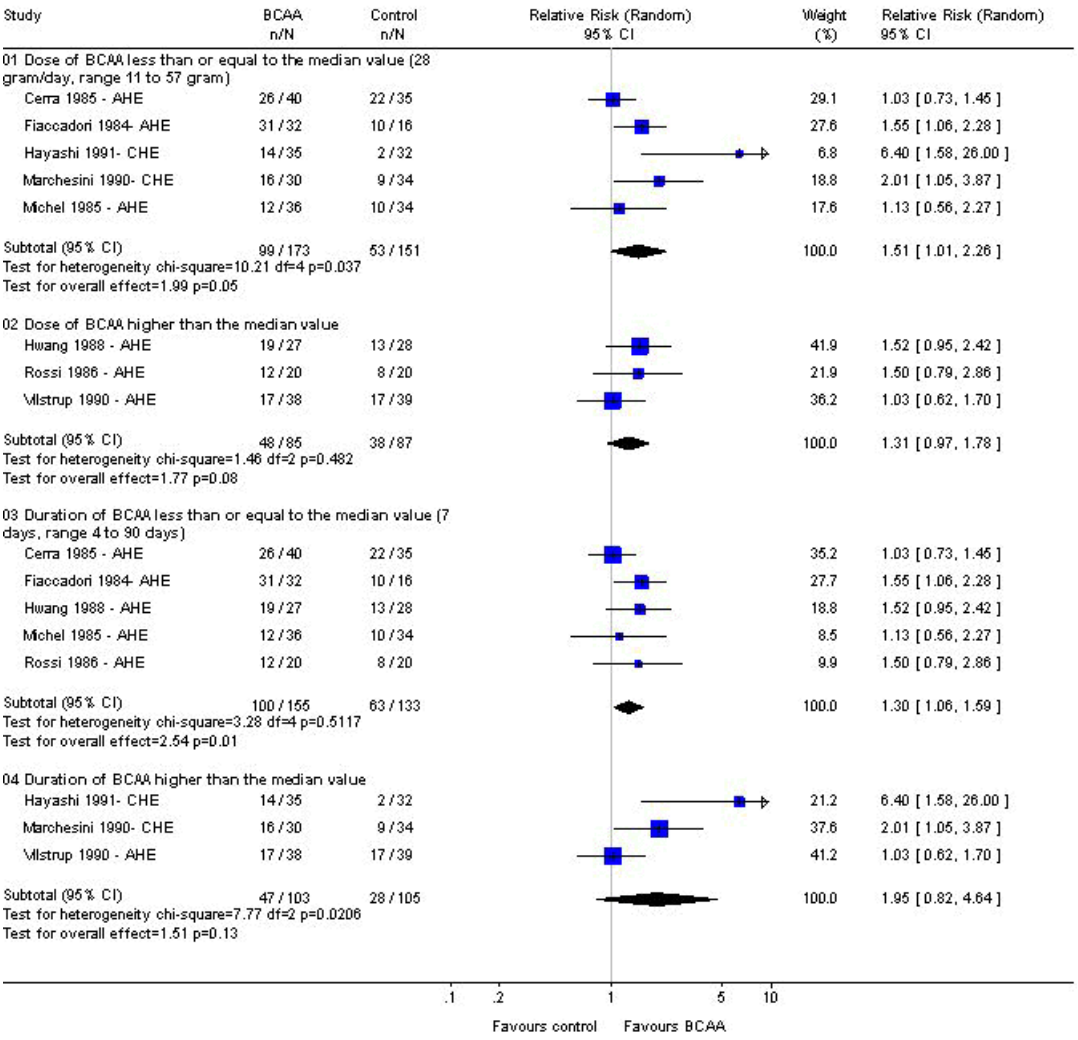
02.02 Form of hepatic encephalopathy and mode of administration - Improvement

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 02 Sensitivity analyses - BCAA versus control (improvement)
Outcome: 02 Form of hepatic encephalopathy and mode of administration - Improvement



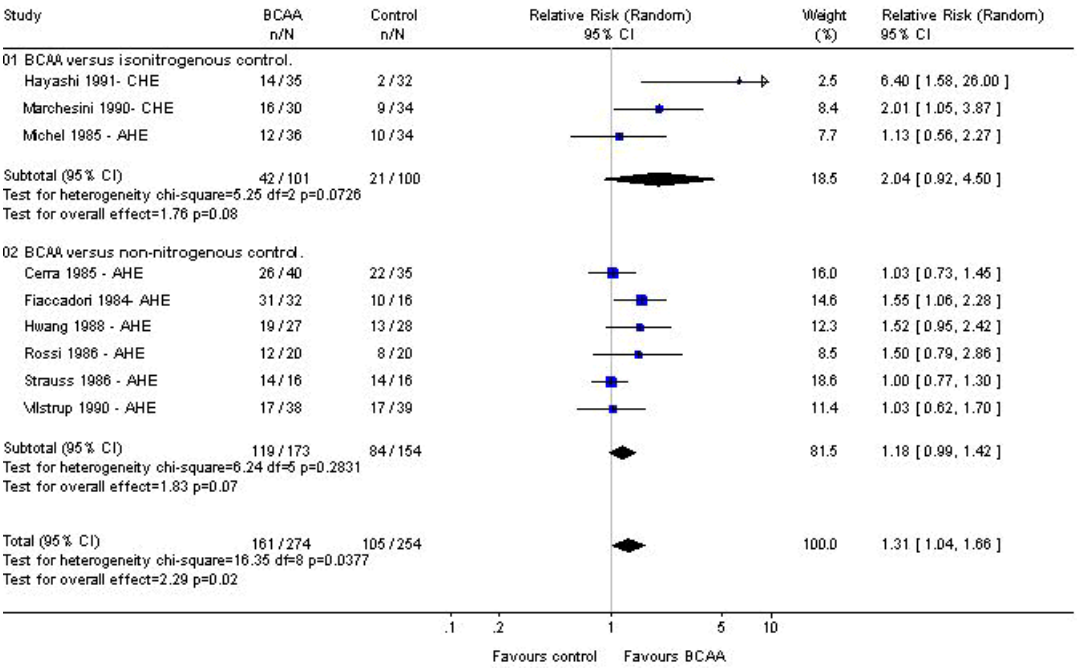
02.03 Dose and duration of BCAA intervention - Improvement

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 02 Sensitivity analyses - BCAA versus control (improvement)
Outcome: 03 Dose and duration of BCAA intervention - Improvement



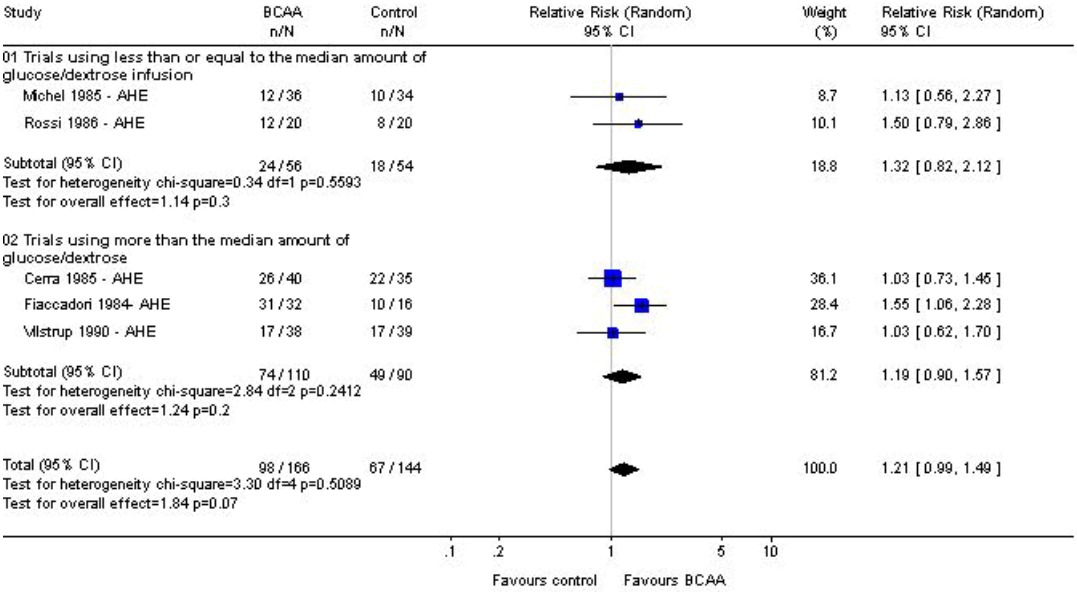
02.04 Isonitrogenous versus non-nitrogenous control - Improvement

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 02 Sensitivity analyses - BCAA versus control (improvement)
Outcome: 04 Isonitrogenous versus non-nitrogenous control - Improvement



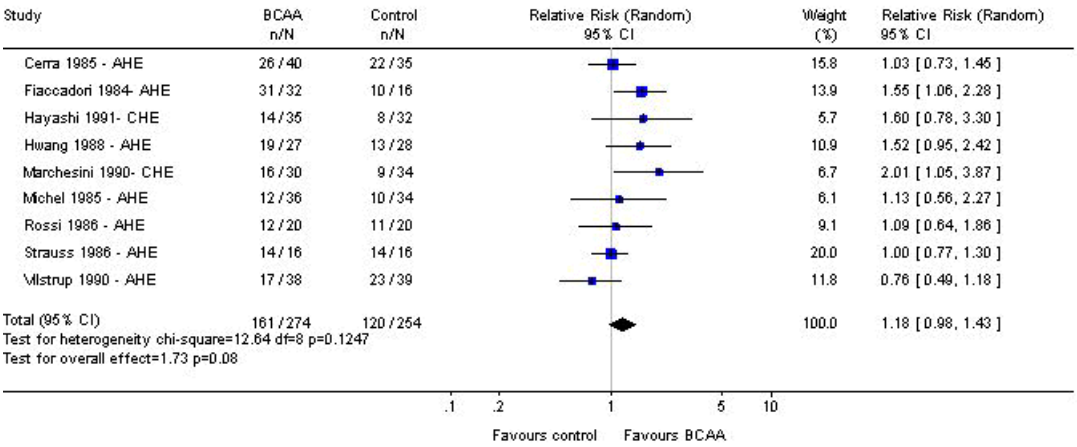
02.05 Amount of glucose/dextrose infusion - Improvement

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 02 Sensitivity analyses - BCAA versus control (improvement)
Outcome: 05 Amount of glucose/dextrose infusion - Improvement



02.06 Worst case scenario favouring control therapy - Improvement

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 02 Sensitivity analyses - BCAA versus control (improvement)
Outcome: 06 Worst case scenario favouring control therapy - Improvement



02.07 Best case scenario favouring BCAA - Improvement

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 02 Sensitivity analyses - BCAA versus control (improvement)
Outcome: 07 Best case scenario favouring BCAA - Improvement

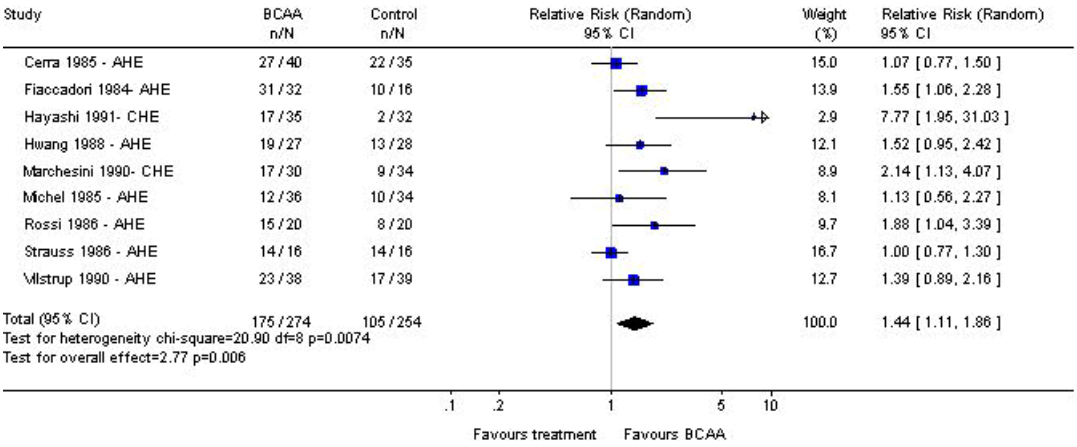
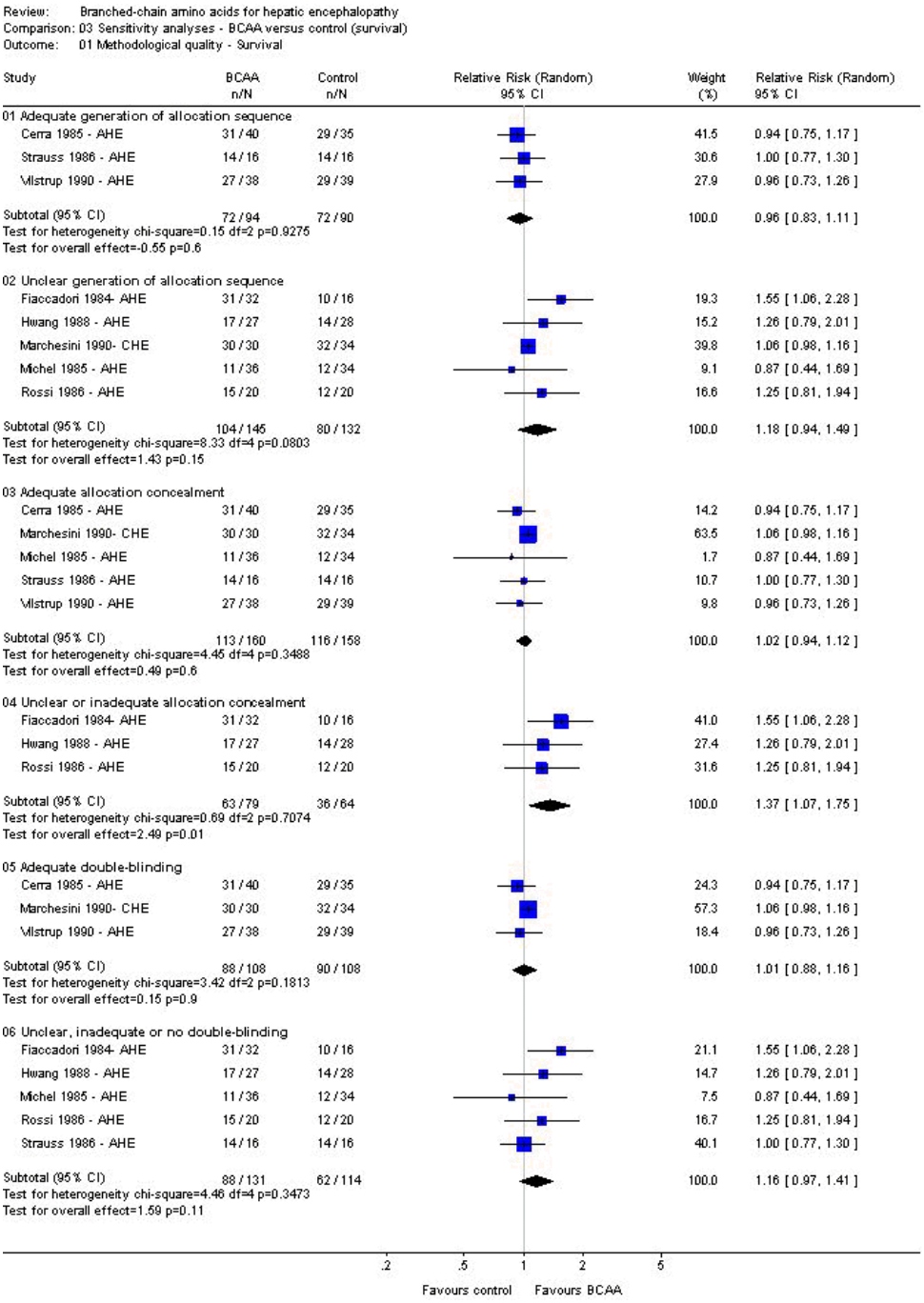


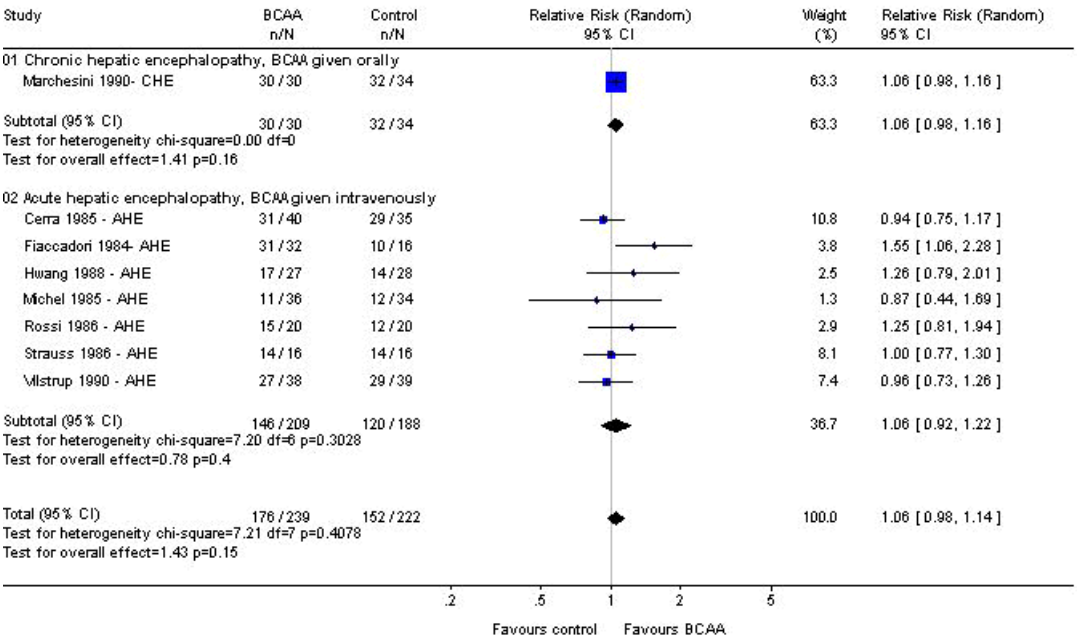
Fig. 03 Sensitivity analyses - BCAA versus control (survival)

03.01 Methodological quality - Survival



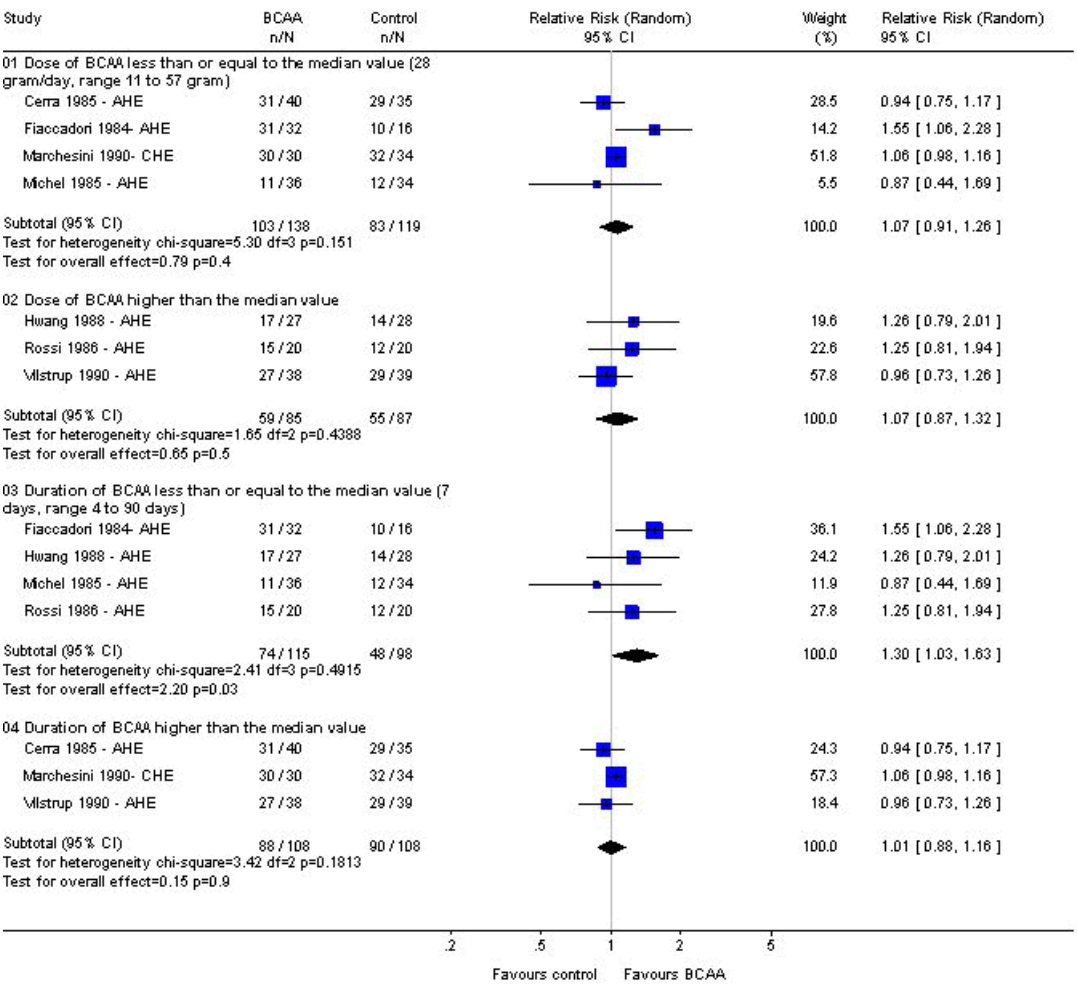
03.02 Form of hepatic encephalopathy and mode of administration - Survival

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 03 Sensitivity analyses - BCAA versus control (survival)
Outcome: 02 Form of hepatic encephalopathy and mode of administration - Survival



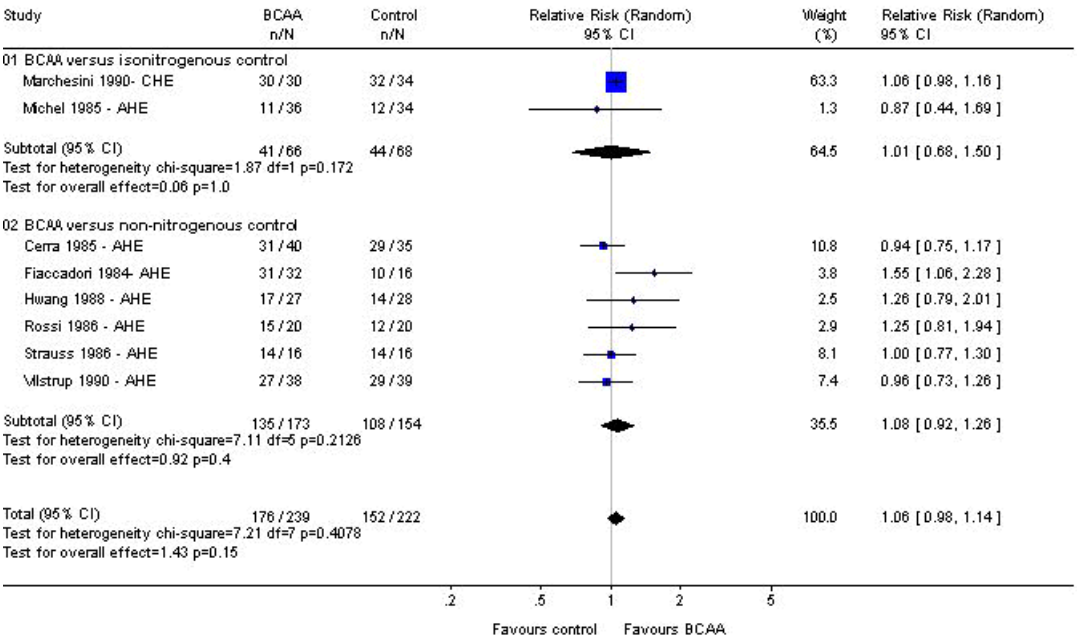
03.03 Dose and duration of BCAA intervention - Survival

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 03 Sensitivity analyses - BCAA versus control (survival)
Outcome: 03 Dose and duration of BCAA intervention - Survival



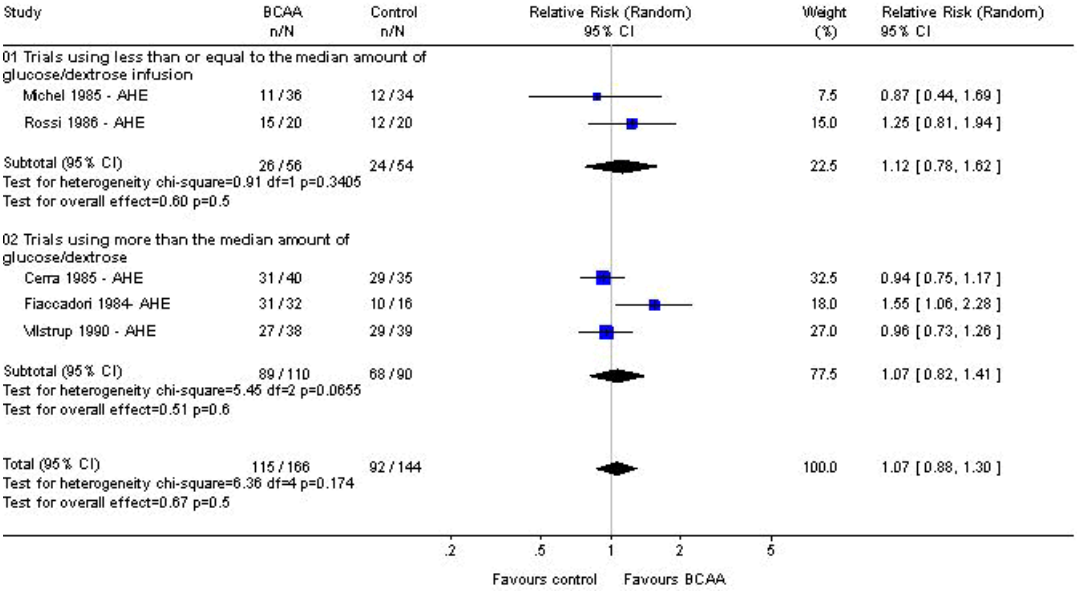
03.04 Isonitrogenous versus non-nitrogenous control - Survival

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 03 Sensitivity analyses - BCAA versus control (survival)
Outcome: 04 Isonitrogenous versus non-nitrogenous control - Survival



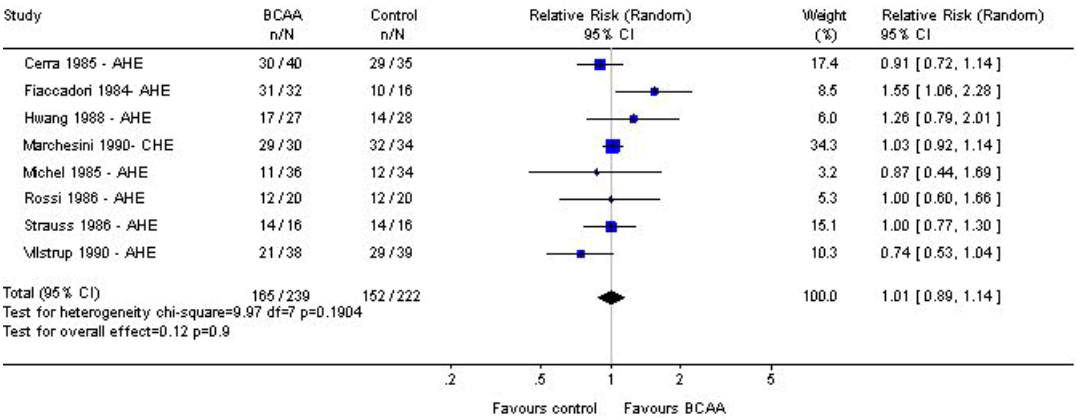
03.05 Amount of glucose/dextrose infusion - Survival

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 03 Sensitivity analyses - BCAA versus control (survival)
Outcome: 05 Amount of glucose/dextrose infusion - Survival



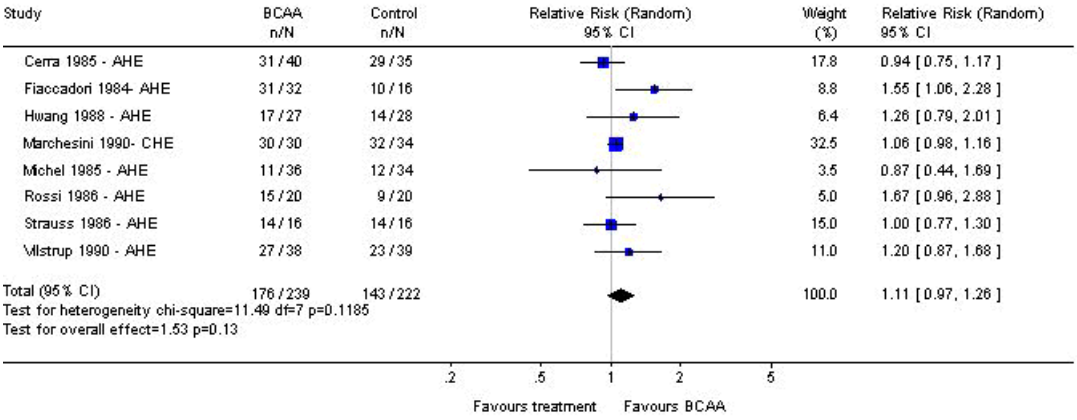
03.06 Worst case scenario favouring control therapy - Survival at maximum follow up

Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 03 Sensitivity analyses - BCAA versus control (survival)
Outcome: 06 Worst case scenario favouring control therapy - Survival at maximum follow up



03.07 Best case scenario favouring BCAA - Survival at maximum follow up

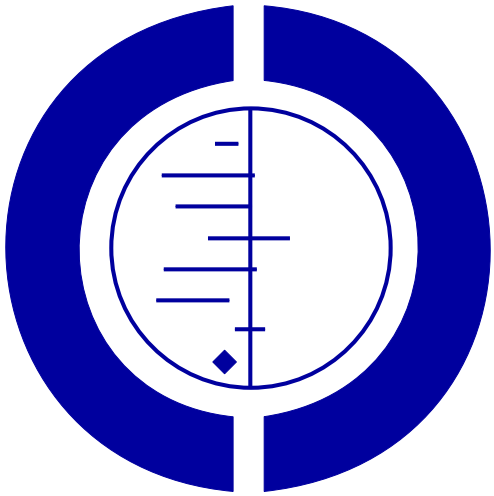
Review: Branched-chain amino acids for hepatic encephalopathy
Comparison: 03 Sensitivity analyses - BCAA versus control (survival)
Outcome: 07 Best case scenario favouring BCAA - Survival at maximum follow up



Paper 4

Dopaminergic agonists for hepatic encephalopathy (Review)

Als-Nielsen B, Gluud LL, Gluud C



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Dopaminergic agonists for hepatic encephalopathy (Review)

Als-Nielsen B, Gluud LL, Gluud C

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ABSTRACT

Background
Hepatic encephalopathy may be associated with an impairment of the dopaminergic neurotransmission. Dopaminergic agonists may therefore have a beneficial effect on patients with hepatic encephalopathy.

Objectives
To evaluate the beneficial and harmful effects of dopaminergic agonists for patients with hepatic encephalopathy.

Search strategy
Trials were identified through *The Cochrane Hepato-Biliary Group Controlled Trials Register* (July 2004), *The Cochrane Central Register of Controlled Trials* (Issue 3, 2004), *MEDLINE* (1966-2004/07), *EMBASE* (1980-2004/07), manual searches of bibliographies and journals, authors of trials, and pharmaceutical companies.

Selection criteria
All randomised trials comparing dopaminergic agonists versus placebo or no intervention for hepatic encephalopathy.

Data collection and analysis
Trial inclusion and data extraction were made independently by two reviewers. Binary outcomes are reported as odds ratios (OR) with 95% confidence intervals (CI) based on a random effects model. The presence of statistical heterogeneity was explored by the chi-squared test with significance set at $P < 0.1$. Potential sources of heterogeneity were explored through subgroup analyses with regard to the type of hepatic encephalopathy and type of dopaminergic agonist.

Main results
Five trials were included. Four trials had low methodological quality. Compared with placebo or no treatment, dopaminergic agonists had no significant effect on the risk of no improvement (OR 0.33, 95% CI 0.01 to 11.25, two trials, 80 patients) or mortality (OR 1.11, 95% CI 0.34 to 3.54, four trials, 139 patients). There was significant heterogeneity ($P = 0.09$) among trial results on the risk of no improvement, but not on mortality ($P = 0.19$). The treatment response was not significantly different with regard to the type of hepatic encephalopathy or dopaminergic agonist, but the analyses had very low power to detect potential differences. There was a nonsignificant trend that dopaminergic agonists may be associated with adverse events (OR 8.33, 95% CI 0.37 to 187. 74, 2 trials, 13 patients). All adverse events (n = 7) occurred in the experimental group.

Authors' conclusions
This review does not provide evidence that dopaminergic agonists are of benefit to patients with acute or chronic hepatic encephalopathy, or fulminant hepatic failure. The review is limited by the small number of trials performed within this field, the low number of patients randomised in each trial, and the low methodological quality of included trials. Accordingly, there is also insufficient evidence to exclude a potential beneficial effect. Dopaminergic agonists should not be used for hepatic encephalopathy, but may be assessed in future randomised clinical trials.

SYNOPSIS

No evidence to support or refute that dopaminergic agonists have an effect on hepatic encephalopathy

Hepatic encephalopathy occurs in patients with chronic liver disease or fulminant liver failure. Hepatic encephalopathy is associated with changes in mental state, ranging from minor signs of altered brain function to deep coma. Treatment with dopaminergic agonists has been proposed to ameliorate the symptoms. This review does not provide any evidence that dopaminergic agonists have an effect on patients with hepatic encephalopathy. Dopaminergic agonists should not be used for hepatic encephalopathy in clinical practice, but may be assessed in future randomised clinical trials.

BACKGROUND

Hepatic encephalopathy is a complex neuropsychiatric syndrome, which may complicate acute or chronic liver failure (Gitlin 1996). It is characterised by changes in mental state including a wide range of neuropsychiatric symptoms, ranging from minor, not readily discernible signs of altered brain function, to deep coma (Conn 1979).

Traditionally, hepatic encephalopathy is considered a reversible metabolic disorder due to the accumulation of toxic agents, which have not been metabolised by the liver (Gitlin 1996). The pathogenesis is however unknown, and several mechanisms have been proposed. Newer research points at an abnormal interaction between the altered astrocyte and other cellular elements (Haussinger 2000; Cordoba 2001). This leads to low grade cerebral edema, which is accompanied by alterations in glioneural communication (Haussinger 2000; Cordoba 2001).

Several hypotheses have been raised as to which toxins mediate hepatic encephalopathy. One of the hypotheses, the false neurotransmitter hypothesis, was raised in the 1970s. It suggests that the pathogenesis involves an imbalance in the amino acid concentrations leading to the accumulation of false neurotransmitters (Fischer 1971; Fischer 1984). These compete with and displace the normal neurotransmitters, which may be associated with an impairment of the dopaminergic neurotransmission. Branched-chain amino acids have been used for balancing the amino acid concentrations, but in a previous systematic review (Als-Nielsen 2003) we found no high-quality evidence of significant beneficial effects.

Although the old neurotransmitter hypothesis is considered obsolete (Lizardi-Cervera 2003), recent studies have rekindled the possible alteration of dopamine neurotransmission in hepatic encephalopathy. A study by Rose et al (Rose 1999) indicates that manganese may deposit in basal ganglia and induce extrapyramidal symptomatology. The presence of extrapyramidal symptoms in patients with cirrhosis, similar to Parkinson's disease, suggests an impairment of dopaminergic neurotransmission (Blei 1999; Jover 2003). Further, recent research has found a correlation between the presence of extrapyramidal symptoms in cirrhosis and alterations in the basal ganglia detected by magnetic resonance imaging and proton spectroscopy (Spahr 2000).

Several uncontrolled trials have suggested that levodopa or bromocriptine could be beneficial in the treatment of hepatic encephalopathy (Parkes 1970; Jorge 1973), but only few randomised clinical trials have been performed (Uribe 1979; Michel 1980; Morgan 1980). The dopaminergic agonists, which have been assessed, are levodopa, a precursor of dopamine, and bromocriptine, a dopamine receptor agonist with a prolonged action. At present, dopaminergic agonists are not part of conventional treatment of hepatic encephalopathy, but several guidelines state that bromocriptine may be indicated for patients with chronic encephalopathy (Blei 1999; Lizardi-Cervera 2003). We have been unable to identify any meta-analyses or systematic reviews on the topic.

OBJECTIVES

To evaluate the beneficial and harmful effects of dopaminergic agonists for patients with hepatic encephalopathy.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

The review included all randomised trials regardless of publication status, language, or blinding. Unpublished trials were included if the methodology and the data could be accessed in written form.

Types of participants

Patients with hepatic encephalopathy in connection with acute or chronic liver diseases or fulminant hepatic failure were included. Patients of either gender, any age or ethnic origin were included,

irrespective of the etiology of the liver disease and the factor(s) precipitating the hepatic encephalopathy. Due to the wide spectrum of symptoms and underlying liver failure, hepatic encephalopathy has traditionally been divided into several categories:

Acute hepatic encephalopathy involves an abrupt onset of neuropsychiatric symptoms in patients with chronic liver disease. Acute hepatic encephalopathy may be idiopathic or precipitated by one or more causes including infections, gastrointestinal bleeding, electrolyte or acid-base disturbances, constipation, medications, hypo- or hyperglycaemia, renal dysfunction, large protein meals, alcohol withdrawal, or a superimposed acute liver disease.

Chronic hepatic encephalopathy involves persistent neuropsychiatric dysfunction in patients with chronic liver disease. The onset is usually insidious and the dysfunction may be clinically overt (i.e., chronic hepatic encephalopathy) or only demonstrable by psychometric testing (ie, minimal hepatic encephalopathy also known as subclinical or latent hepatic encephalopathy).

Fulminant hepatic failure is a severe stage of hepatic functional deterioration in patients without underlying liver disease. The main clinical features are hepatic encephalopathy and direct symptoms of liver cell damage, mainly jaundice and coagulation disorders (Bernuau 1999).

Types of intervention

Dopaminergic agonists (eg, levodopa or bromocriptine) in any dose or duration compared with placebo or no intervention. Additional interventions were allowed, if received by both intervention and control groups.

Types of outcome measures

The following outcomes were assessed at the end of treatment:

- Number of patients without improvement of hepatic encephalopathy. Improvement was defined as partial or complete resolution of clinical or subclinical symptoms of hepatic encephalopathy. Improvement could be assessed by clinical grading, electrophysiological testing, psychometrical testing, or summary gradings including the Portal-systemic Encephalopathy Index (Conn 1977; Blei 1999).
- Mortality.
- Number and type of adverse events. Adverse events were graded as serious or non-serious according to the International Conference on Harmonisation Guidelines (ICH-GCP 1997).
- Quality of life.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Hepato-Biliary Group search strategy

The Cochrane Hepato-Biliary Group Controlled Trials Register, *The Cochrane Central Register of Controlled Trials (CENTRAL)*, *MEDLINE* on SilverPlatter, and *EMBASE* were searched July 22, 2004 using the search strategies specified in Table 01.
The reference lists of relevant articles were scanned for additional trials. The principal authors of the identified clinical trials and pharmaceutical companies involved in the production of dopaminergic agonists were inquired about additional trials they might know of.

METHODS OF THE REVIEW

Selection of trials

Decisions on which trials to include were taken independently by BAN and LLG. The selection was performed unblinded with regard to the names of the authors, investigators, institution, source, and results. Disagreements were resolved by discussion. All eligible trials were listed and excluded trials were identified with the reason for exclusion.

Methodological quality

BAN and LLG evaluated independently the methodological quality of each trial. We assessed the methodological quality by the following components (Jadad 1996; Schulz 1995; Moher 1998; Kjaergard 2001).

Generation of the allocation sequence

- Adequate: by table of random numbers, computer generated random numbers, coin tossing, shuffling or similar.
- Unclear: if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate: if a system involving dates, names, or admittance numbers were used for the allocation of patients. Such trials were excluded from the review.

Allocation concealment

- Adequate: if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear: if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Double blinding

- Adequate: if the trial was described as double blind and the method of blinding involved identical placebo or active drugs.
- Unclear: if the trial was described as double blind, but the method of blinding was not described.
- Not performed: if the trial was not double blind or the method of blinding was inappropriate.

Follow-up

- Adequate: if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear: if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate: if the number or reasons for dropouts and withdrawals were not described.

Intention-to-treat analysis

- Adequate: if all randomised participants were included in the analysis in the group to which they originally were assigned.
- Unclear: if the report gave the impression that all participants were included in the analysis.
- Inadequate: if randomised participants were excluded from the analysis.

We extracted whether sample size calculations were reported and whether pre-set sample size was obtained. We classified trials with adequate allocation concealment and adequate blinding as high quality.

Data extraction

Two reviewers (BAN and LLG) independently extracted data from each trial. Primary investigators were contacted if data were missing. We extracted whether the trial used a parallel or crossover design, methodological quality, type and etiology of the underlying liver diseases, type of hepatic encephalopathy (acute, chronic, or fulminant hepatic failure), mean age, proportion of men, number of patients randomised, type, dose and duration of therapy, mode of administration, type of additional intervention(s), number of dropouts, and whether the trial assessed health economics.

Quantitative data synthesis

All analyses were if possible performed according to the intention-to-treat method, ie, including all randomised patients irrespective of compliance or follow-up. If patients had missing outcome data, we used the last reported observed response ('carry forward') (Hollis 1999). The statistical package (RevMan Analyses 1.0.1) provided by The Cochrane Collaboration was used.

Data from the first treatment period in crossover trials were preferably included in meta-analyses, but we also performed meta-analyses including the paired data by the method developed by Becker and Balagtas (Becker 1993). Binary outcomes were expressed as odds ratios (OR) with 95% confidence intervals (CI). We used a random effects model (DerSimonian 1986) due to anticipated variability between trials regarding patients and interventions.

The presence of statistical heterogeneity was explored by the chi-squared test with significance set at $P < 0.1$. The percentage of variation between trial results that is due to heterogeneity rather than chance was measured by I2 (Higgins 2003). Potential sources of heterogeneity were explored through subgroup analyses with regard to the methodological quality, type of dopaminergic agonist, type of hepatic encephalopathy, underlying cause of liver disease,+ and precipitating factors. We used the test of interaction (Altman 2003) to compare the difference between the estimates of subgroup analyses.

DESCRIPTION OF STUDIES

Search results

Figure 01 summarises the literature search. A total of 111 references were identified in *The Cochrane Hepato-Biliary Group Controlled Trials Register* (n = 6), *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) (n = 19), *MEDLINE* (n = 12), *EMBASE* (n = 69), and reference lists (n = 5). We excluded 26 duplicates and 65 clearly irrelevant references by reading abstracts. We retrieved 20 references for further assessment. Of these, we excluded 12 references because they were not randomised (n = 7), did not assess hepatic encephalopathy (n = 1), did not assess a dopaminergic agonist (n = 1), control group received active treatment (n = 2), or was a narrative review (n = 1). Excluded studies are listed under 'Characteristics of excluded studies' with reasons for exclusion. The remaining eight references referred to five randomised trials, which were included in the review.

Trial characteristics

The five included trials (Vij 1979; Uribe 1979; Michel 1980; Morgan 1980; Koshy 1982) were all reported in full articles. Three trials on acute hepatic encephalopathy (Michel 1980) and fulminant hepatic failure (Vij 1979; Koshy 1982) used a parallel group design and two trials on chronic hepatic encephalopathy a crossover design (Uribe 1979; Morgan 1980). A total of 144 patients were randomised. In the trials reporting data on gender, 80% of the patients were men. The median number of patients in each trial was 16 (range 5 to 75). The mean ages ranged from 32 to 57 years (median 51 years). One trial assessed levodopa versus placebo in 75 patients with cirrhosis and acute hepatic encephalopathy (Michel 1980), two trials assessed bromocriptine versus placebo in 13 patients with cirrhosis and chronic hepatic encephalopathy (Uribe 1979; Morgan 1980), and two trials assessed levodopa plus "standard hepatic encephalopathy regime" versus "standard hepatic encephalopathy regime" in 56 patients with fulminant hepatic failure (Vij 1979; Koshy 1982). The aetiology of cirrhosis was alcohol (77%), viral hepatitis (16%), and other reasons (7%). Fulminant hepatic failure was in all cases due to viral hepatitis. The daily mean dose of levodopa was four gram and of bromocriptine 15 gram. The median duration of treatment was 14 days (range 7 to 56 days). None of the trials followed patients after the end of treatment.

METHODOLOGICAL QUALITY

Only one trial had high quality (Morgan 1980). All trials were described as randomised, but an adequate method of generating the allocation sequence was reported through personal communications for only two trials (Uribe 1979; Morgan 1980). Treatment allocation was adequately concealed in one trial (Morgan 1980). Double blinding was reported for three trials (Uribe 1979; Michel 1980; Morgan 1980). Follow-up was adequately described in two trials (Uribe 1979; Morgan 1980), and intention-to-treat analy-

ses were performed in one trial (Morgan 1980). In three trials, dropouts and withdrawals were not mentioned, giving the impression that there had been no dropouts and that all randomised patients were included in the analyses (Vij 1979; Michel 1980; Koshy 1982). None of the trials reported sample size calculations.

RESULTS

Compared with placebo or no treatment, dopaminergic agonists had no significant effect on the risk of no improvement of hepatic encephalopathy (odds ratio (OR) 0.33, 95% confidence interval (CI) 0.01 to 11.25, two trials, 80 patients) or mortality (OR 1.11, 95% CI 0.34 to 3.54, four trials, 139 patients). There was no significant heterogeneity among trial results on mortality (P = 0.19, I2 = 28%). There was significant heterogeneity (P = 0.09) on the risk of no improvement between the parallel group trial assessing levodopa for acute hepatic encephalopathy (Michel 1980) and the first treatment period result from a crossover trial assessing bromocriptine for chronic hepatic encephalopathy (Morgan 1980). The variability across trials was substantial (I2 = 66%). In the analysis including paired data from crossover trials we were able to include an additional trial (Uribe 1979). The result of this analysis (OR 0.68; 95% CI 0.17 to 2.67, three trials, 88 patients) did not change the overall result, but the amount of heterogeneity and variability decreased (P = 0.19; I2 = 40%).

Adverse events were reported in two trials (Uribe 1979; Morgan 1980) and occurred in seven out of 13 patients. None of them were serious. All adverse events occurred in the experimental group and included hypomania (n = 1), hallucinations and headache (n = 1), constipation (n =3), and nausea and vomiting (n = 2), but the occurrence was not significantly more frequent in the patients receiving dopaminergic agonists compared to placebo (OR 8.33, 95% CI 0.37 to 187.74).

There was no significant difference in treatment response between high and low quality trials (P = 0.1 by test of interaction) or between the parallel group trial assessing levodopa for acute hepatic encephalopathy and the crossover trials assessing bromocriptine for chronic hepatic encephalopathy (P = 0.27 by test of interaction). Due to lack of data we did not perform planned subgroup analyses with regard to underlying cause of liver disease and precipitating factors.

None of the trials reported data on quality of life.

DISCUSSION

This review does not provide any evidence that dopaminergic agonists are of benefit to patients with acute or chronic hepatic encephalopathy, or fulminant hepatic failure. There was a nonsignificant trend that dopaminergic agonists may be associated with adverse events. However, the review is limited by the small number of trials performed within this field, the low number of patients randomised in each trial, and the low methodological quality of included trials. Accordingly, there is also insufficient evidence to exclude a potential beneficial effect.

The treatment response was not different in different types of hepatic encephalopathy. Dopaminergic agonists did neither significantly improve patients with either acute or chronic hepatic encephalopathy nor did they significantly affect mortality rates in patients with fulminant hepatic failure. However, far too few patients have been randomised to reliably exclude that the treatment response could be different according to the type of hepatic encephalopathy.

Based on data from Parkinson's disease (Miyasaki 2002), the identified trials seemed to use levodopa and bromocriptine in sufficient doses for a reasonable duration of time in order to expect a clinical response. Other dopaminergic agonists exist (Miyasaki 2002), but these have not been assessed in trials on hepatic encephalopathy. The rationale for assessing dopaminergic agonists for hepatic encephalopathy was based on the old 'false neurotransmitter' hypothesis (Fischer 1971). Although we found no high-quality evidence that branched-chain amino acids have a significant beneficial effect on patients with hepatic encephalopathy (Als-Nielsen 2003), recent studies have rekindled the possible alteration of dopamine neurotransmission. New studies have shown presence of extrapyramidal symptoms in patients with cirrhosis (Jover 2003) and correlation between the symptoms and alterations in the basal ganglia, detected by magnetic resonance imaging and proton spectroscopy (Spahr 2000), similar to Parkinson's disease.

The two trials on chronic hepatic encephalopathy used a crossover design. However, because of the spontaneously fluctuating nature of hepatic encephalopathy (Basile 1991), the crossover design does not seem appropriate when assessing interventions for hepatic encephalopathy. Patients' underlying condition and ability to respond to treatment may not remain stable from the first to the second treatment period. Nevertheless, this design is widely used in this field. In a previous systematic review on flumazenil for hepatic encephalopathy (Als-Nielsen 2001), 8/12 included trials were crossover trials. Therefore, we did not exclude a priori such trials from the current systematic review, but attempted to include the results from the first treatment period. However, these data could only be extracted from one trial (Morgan 1980) and the meta-analysis including these data revealed significant heterogeneity. By including the paired data from crossover trials (Elbourne 2002), we were also able to include the trial by Uribe et al. (Uribe 1979). Although the overall results did not change significantly, this approach appeared to be associated with less heterogeneity.

Further, if only looking at the meta-analysis including results from the first period, one could suspect that the treatment response between either acute and chronic, or levodopa and bromocriptine, was different. Including the trial by Uribe et al. (Uribe 1979) revealed that this did not appear to be the case. Rather, the heterogeneity was due to a single, small, very positive trial (Morgan 1980). This trial was the only high-quality trial, which is surprising, considering previous studies showing that trials with high

quality tend to reach more conservative results than low-quality trials (Schulz 1995; Jadad 1996; Moher 1998; Kjaergard 2001; Als-Nielsen 2004b). Still, this finding is in accordance with studies showing that the smaller the study the larger the treatment effect (Wood 2003; Ioannidis 2003; Als-Nielsen 2004c).

Two small, low quality, crossover trials on chronic hepatic encephalopathy compared bromocriptine with lactulose (Messner 1982) or neomycin (Uribe 1983). Together, the two trials randomised 15 patients, which is far too few to establish with confidence whether bromocriptine has comparable effect to lactulose or neomycin. In addition, it is not appropriate to compare new treatments for hepatic encephalopathy with treatments that have not been proved to have beneficial effect on hepatic encephalopathy (Als-Nielsen 2004a). Both nonabsorbable disaccharides and antibiotics have been introduced into clinical practice without appropriate documentation (Als-Nielsen 2004a).

The clinical intervention research on hepatic encephalopathy is flawed by the lack of shared definitions. The clinical conditions that are summarised under the term 'hepatic encephalopathy' are highly heterogeneous and the methods used to quantitate treatment effects and treatment outcomes are highly variable. This may in part explain the variability across trial results. In general, the scales and items used for assessing hepatic encephalopathy are arbitrary and not tested for reliability or validity. There is a substantial need for clear definitions and diagnostic criteria of hepatic encephalopathy as well as a reassessment and validation of the various scales and items using sound methodological approaches (Streiner 1995). A step in this direction has been the recently published consensus statement regarding hepatic encephalopathy on new terminology, definition, and diagnostic criteria (Ferenci 2002).

Dopaminergic agonists are not part of conventional treatment of hepatic encephalopathy, but guidelines state that bromocriptine may be indicated for patients with chronic encephalopathy, unresponsive to other therapy (Blei 1999). This review shows that there is no evidence to support the use of dopaminergic agonists for hepatic encephalopathy. Overall, the available data do not seem promising. Considering the limited amount of evidence (Als-Nielsen 2004a) concerning the efficacy of interventions frequently used for hepatic encephalopathy (eg, nonabsorbable disaccharides or nonabsorbable antibiotics), it would seem to be more important to perform randomised trials assessing the beneficial and harmful effects of these interventions.

AUTHORS' CONCLUSIONS

Implications for practice

This review does not provide evidence to support or refute that dopaminergic agonists have an effect on acute or chronic hepatic encephalopathy or fulminant hepatic failure. Accordingly, dopaminergic agonists for hepatic encephalopathy should not be used in clinical practice.

Implications for research

The available data do not seem promising. Considering the limited amount of evidence concerning the efficacy of treatments frequently used for hepatic encephalopathy, it would seem to be more important to conduct randomised trials to establish for eg, whether nonabsorbable disaccharides or nonabsorbable antibiotics have beneficial effects on hepatic encephalopathy. However, if researchers wish to conduct more trials on dopaminergic agonists for hepatic encephalopathy, they should perform adequately powered high-quality trials. Trials should use a parallel group design, due to the spontaneously fluctuating nature of hepatic encephalopathy. Trials should use placebo as comparator, employ an independent Data Monitoring and Safety Committee in order to monitor the balance between potential benefits and harms, and report the results according to the CONSORT statement (www.consort-statement.org).

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POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Koshy 1982
Methods	Parallel group trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: not performed. Follow-up: unclear. Intention to treat analyses: unclear. Sample size estimation: no.
Participants	40 patients with fulminant hepatic failure were randomised. Mean age: not reported. Aetiology of fulminant hepatic failure: viral hepatitis 100%. Proportion of men: not reported.
Interventions	Experimental: levodopa 4 gram/day + standard HE regime. Control: standard HE regime (including neomycin). Treatment duration: not reported.

Outcomes	Mortality.
Notes	Number of dropouts: uncertain. Health economics: not assessed.
Allocation concealment	B

Study	**Michel 1980**
Methods	Parallel group trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: adequate, double blinded using placebo. Follow-up: unclear. Intention to treat analyses: unclear. Sample size estimation: no.
Participants	75 patients with cirrhosis and acute hepatic encephalopathy were randomised. Mean age: 57 years. Aetiology of cirrhosis: alcohol 80%, viral hepatitis 15%, cryptogenic 5%. Proportion of men: 80%
Interventions	Experimental 1: levodopa (2 gram on day 1, 4 gram/day the next 6 days). Experimental 2: levodopa (as above) + dopa-decarboxylase inhibitor (0.2 gram on day 1, 0.4 gram the next 6 days). Control: placebo. Additional therapy: all patients received enemas and magnesium sulfate. Treatment duration: 7 days.
Outcomes	Clinical improvement. Mortality. Electroencephalogram.
Notes	Number of dropouts: uncertain. Health economics: not assessed.
Allocation concealment	B

Study	**Morgan 1980**
Methods	Crossover trial. Generation of the allocation sequence: adequate using a computer-generated random sequence. Allocation concealment: adequate, controlled by hospital pharmacy. Blinding: adequate, double blinded using placebo. Follow-up: adequate. Intention to treat analyses: adequate. Sample size estimation: no.
Participants	Five patients with cirrhosis and chronic hepatic encephalopathy were randomised.

	Mean age: 51 years. Aetiology of cirrhosis: alcohol 60%, cryptogenic 40%. Proportion of men: 100%
Interventions	Experimental: bromocriptine 15 mg/day. Control: placebo (lactose). Additional therapy: all patients received 40 ml lactulose/day. Treatment duration: 8 weeks in each period with no washout period.
Outcomes	Clinical improvement. Adverse events.
Notes	Number of dropouts: 0. Health economics: not assessed.
Allocation concealment	A

Study	**Uribe 1979**
Methods	Crossover trial. Generation of the allocation sequence: adequate using a random numbers table. Allocation concealment: unclear. Blinding: adequate, double blinded using placebo + statistician was blinded. Follow-up: adequate. Intention to treat analyses: inadequate. Sample size estimation: no.
Participants	Eight patients with cirrhosis and chronic hepatic encephalopathy were randomised. Age: ranged from 45-78 years. Aetiology of cirrhosis: alcohol 63%, viral hepatitis 37%. Proportion of men: 63%
Interventions	Experimental: bromocriptine 15 mg/day. Control: placebo (glucose). Additional therapy: none. Treatment duration: 2 weeks in each period, 10 days washout period before trial start and between the two periods.
Outcomes	Clinical improvement. Number connection test. Asterixis. Arterial ammonia. Adverse events.
Notes	Number of dropouts: 1 patient died in the first treatment period while receiving placebo. Health economics: not assessed.
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	Vij 1979
Methods	Parallel group trial. Generation of the allocation sequence: unclear. Allocation concealment: unclear. Blinding: not performed. Follow-up: unclear. Intention to treat analyses: unclear. Sample size estimation: no.
Participants	16 patients with fulminant hepatic failure were randomised. Mean age: 32 years. Aetiology of fulminant hepatic failure: viral hepatitis 100%. Proportion of men: not reported.
Interventions	Experimental: levodopa 3-4 gram/day + supportive therapy. Control: supportive therapy (included 6 gram ampicillin, 2 bowel washes, vitamins, lactobacilli acidophilus, infusion of electrolytes). Treatment duration: not reported.
Outcomes	Mortality.
Notes	Number of dropouts: uncertain. Health economics: not assessed.
Allocation concealment	B

Characteristics of excluded studies

Burroughs 1985	Randomised trial assessing the effect of bromocriptine for alcohol withdrawal symptoms. Excluded because patients did not have hepatic encephalopathy at entry and this was not assessed as an outcome.
Catalano 1982	Controlled crossover study including five patients with chronic hepatic encephalopathy comparing bromocriptine + lactulose, levodopabenserazide + lactulose, and lactulose during five treatment periods. Excluded because the study does not appear to be randomised. We have contacted the authors, but have not obtained a response yet. We urge anyone with knowledge about the design of this study to contact us with information on the design.
Datta 1976	Observational study on four patients with fulminant hepatic failure given L-dopa. Excluded due to lack of randomisation.
Jorge 1973	Observational study on three patients with hepatic encephalopathy given levodopa. Excluded due to lack of randomisation.
Lunzer 1974	Controlled crossover study including three patients with chronic hepatic encephalopathy comparing levodopa with placebo. Excluded because the study does not appear to be randomised. We have contacted the authors, but have not obtained a response yet. We urge anyone with knowledge about the design of this study to contact us with information on the design.
Messner 1982	Randomised crossover trial including 11 patients with chronic hepatic encephalopathy comparing bromocriptine with lactulose. Excluded because the control group received lactulose.

Characteristics of excluded studies (*Continued*)

Pascual 1979	Controlled crossover study including seven patients with chronic hepatic encephalopathy comparing bromocriptine with placebo. Excluded because the study does not appear to be randomised. We have contacted the authors, but have not obtained a response yet. We urge anyone with knowledge about the design of this study to contact us with information on the design.
Trovato 1982	Controlled crossover study including ten patients with chronic hepatic encephalopathy comparing amantadine + lactulose, levodopabenserazide + lactulose, and lactulose during six treatment periods. Excluded because the study does not appear to be randomised. We have contacted the authors, but have not obtained a response yet. We urge anyone with knowledge about the design of this study to contact us with information on the design.
Ubiria 1980	Controlled crossover study including six patients with chronic hepatic encephalopathy comparing bromocriptine with placebo during four treatment periods. Excluded due to lack of randomisation.
Uribe 1982	Randomised trial assessing the effect of metoclopramide, a dopamine-antagonist, in four patients with cirrhosis and hepatic encephalopathy. Excluded because the experimental group did not receive a dopamine agonist.
Uribe 1983	Randomised crossover trial including four patients with chronic hepatic encephalopathy comparing bromocriptine with neomycin. Excluded because the control group received antibiotics.
Uribe 1984	Narrative review.

ADDITIONAL TABLES

Table 01 Search strategies

CHBG-CTR	CENTRAL	MEDLINE	EMBASE

explode all trees (MeSH) #13 (liver next cirrhosis) #14 (hepatic next encephalopathy) #15 (#11 or #12 or #13 or #14) #16 (#10 and #15)	liver cirrhosis hepatic encephalopathy #11 or #12 or #13 or #14 #10 and #15 random* or blind* or placebo* or meta-analysis #16 and #17	liver cirrhosis hepatic encephalopathy #11 or #12 or #13 or #14 #10 and #15 random* or blind* or placebo* or meta-analysis #16 and #17

GRAPHS

Comparison 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients without improvement - including data from 1. treatment period in crossover trials	2	80	Odds Ratio (Random) 95% CI	0.33 [0.01, 11.25]
02 Number of patients without improvement - including paired data from crossover trials	3	6	OR (Random) 95% CI	0.68 [0.17, 2.67]
03 Mortality	4	139	Odds Ratio (Random) 95% CI	1.11 [0.35, 3.54]
04 Adverse events	2	4	OR (Random) 95% CI	8.33 [0.37, 187.76]
05 Sensitivity analysis - methodological quality, number of patients without improvement	3	6	OR (Random) 95% CI	0.68 [0.17, 2.67]

COVER SHEET

Title	Dopaminergic agonists for hepatic encephalopathy
Authors	Als-Nielsen B, Gluud LL, Gluud C
Contribution of author(s)	Bodil Als-Nielsen drafted the protocol, identified trials, extracted data, performed the statistical analyses, and drafted the review. Lise Lotte Gluud selected trials for inclusion and extracted data. All reviewers contributed to the writing of the protocol and review and all have approved of the final version.
Issue protocol first published	2001/2
Review first published	2004/4
Date of most recent amendment	24 August 2004
Date of most recent SUBSTANTIVE amendment	24 August 2004
What's New	Changes to the original protocol: We have changed the term "dopaminergic agents" to 'dopaminergic agonists' (ie, drugs that bind to and activate dopamine receptors) throughout the review.

In 'Types of outcome measures' we have omitted the outcome 'Number of patients with recovery' because it is part of our outcome: 'Number of patients with improvement of hepatic encephalopathy'. We have omitted the outcome measure 'Health economics', but have extracted whether trials assessed this aspect in the trial reports.
We extended the assessment of methodological quality by including assessment of follow-up, intention-to-treat analyses, and sample size calculations. Further, the definitions of the quality components have been elaborated according to the latest recommendations of The Cochrane Hepato-Biliary Group (Gluud 2004).
We performed our analyses based on a random effects model due to anticipated variability between trials regarding patient populations and interventions. The results did not differ significantly when analyses were performed using a fixed effect model.

Date new studies sought but none found

Information not supplied by author

Date new studies found but not yet included/excluded

Information not supplied by author

Date new studies found and included/excluded

22 July 2004

Date authors' conclusions section amended

Information not supplied by author

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GRAPHS AND OTHER TABLES

Fig. 1.

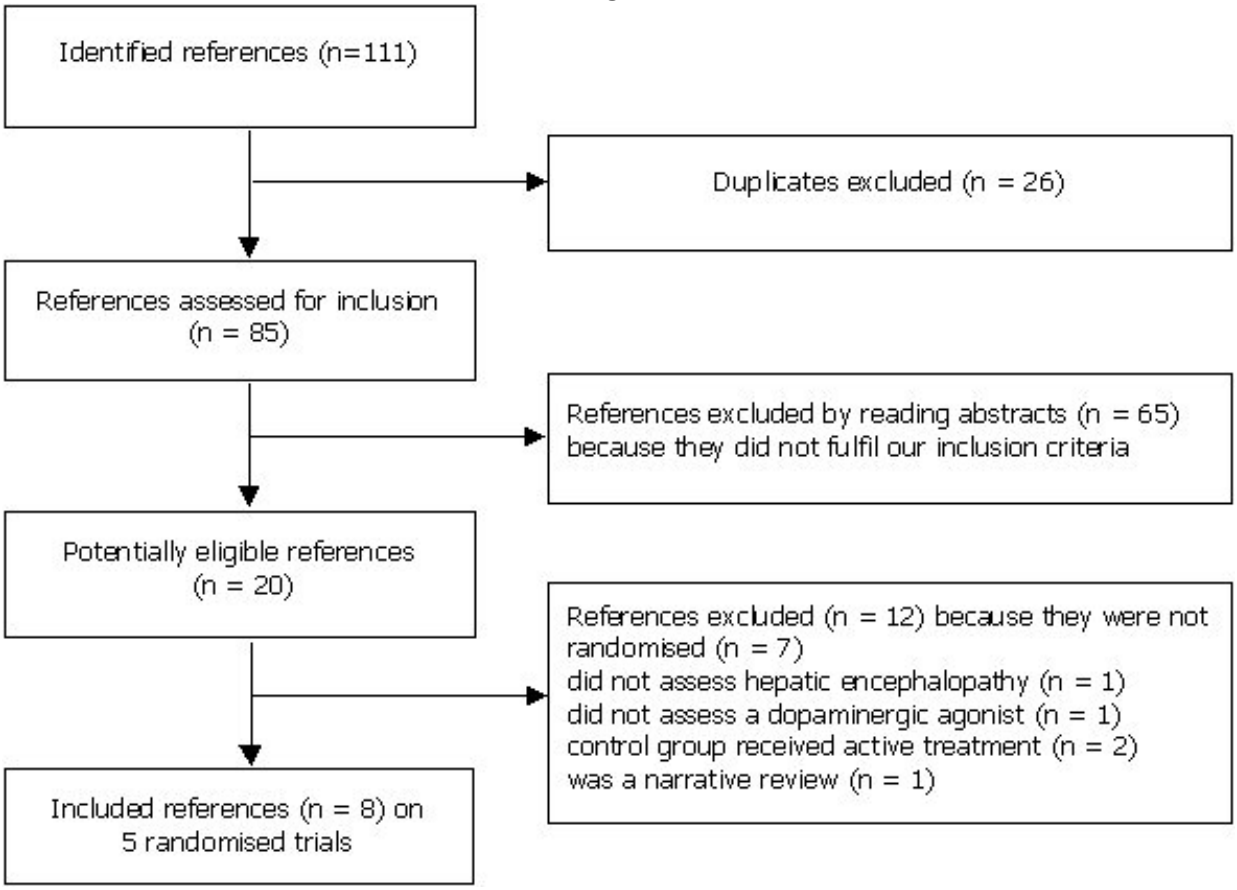


Fig. 2. Comparison 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

01.01 Number of patients without improvement - including data from 1. treatment period in crossover trials

Review: Dopaminergic agonists for hepatic encephalopathy

Comparison: 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

Outcome: 01 Number of patients without improvement - including data from 1. treatment period in crossover trials

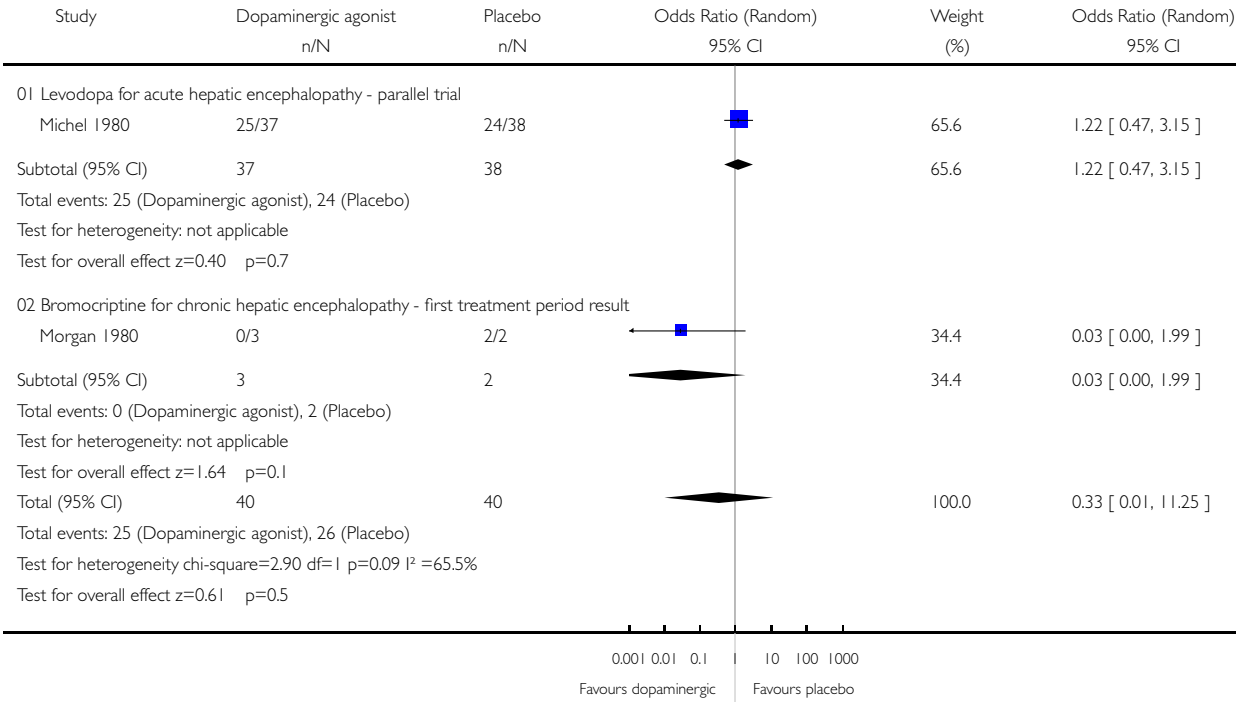


Fig. 3. Comparison 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

01.02 Number of patients without improvement - including paired data from crossover trials

Review: Dopaminergic agonists for hepatic encephalopathy

Comparison: 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

Outcome: 02 Number of patients without improvement - including paired data from crossover trials

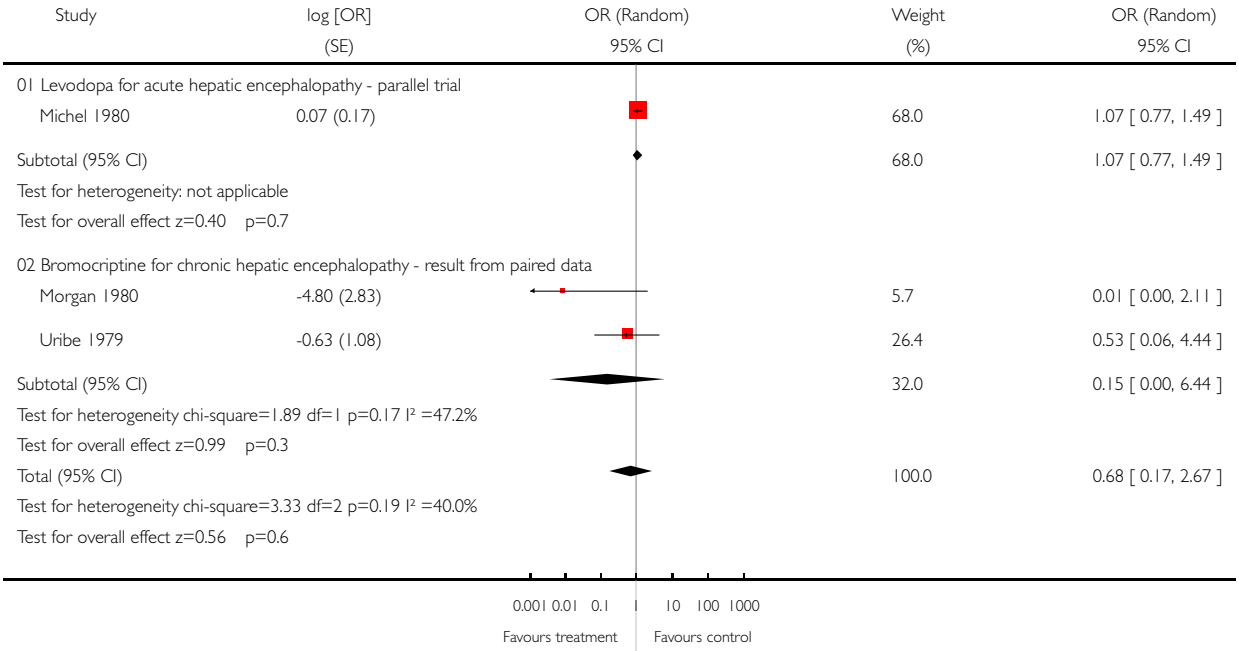


Fig. 4. Comparison 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

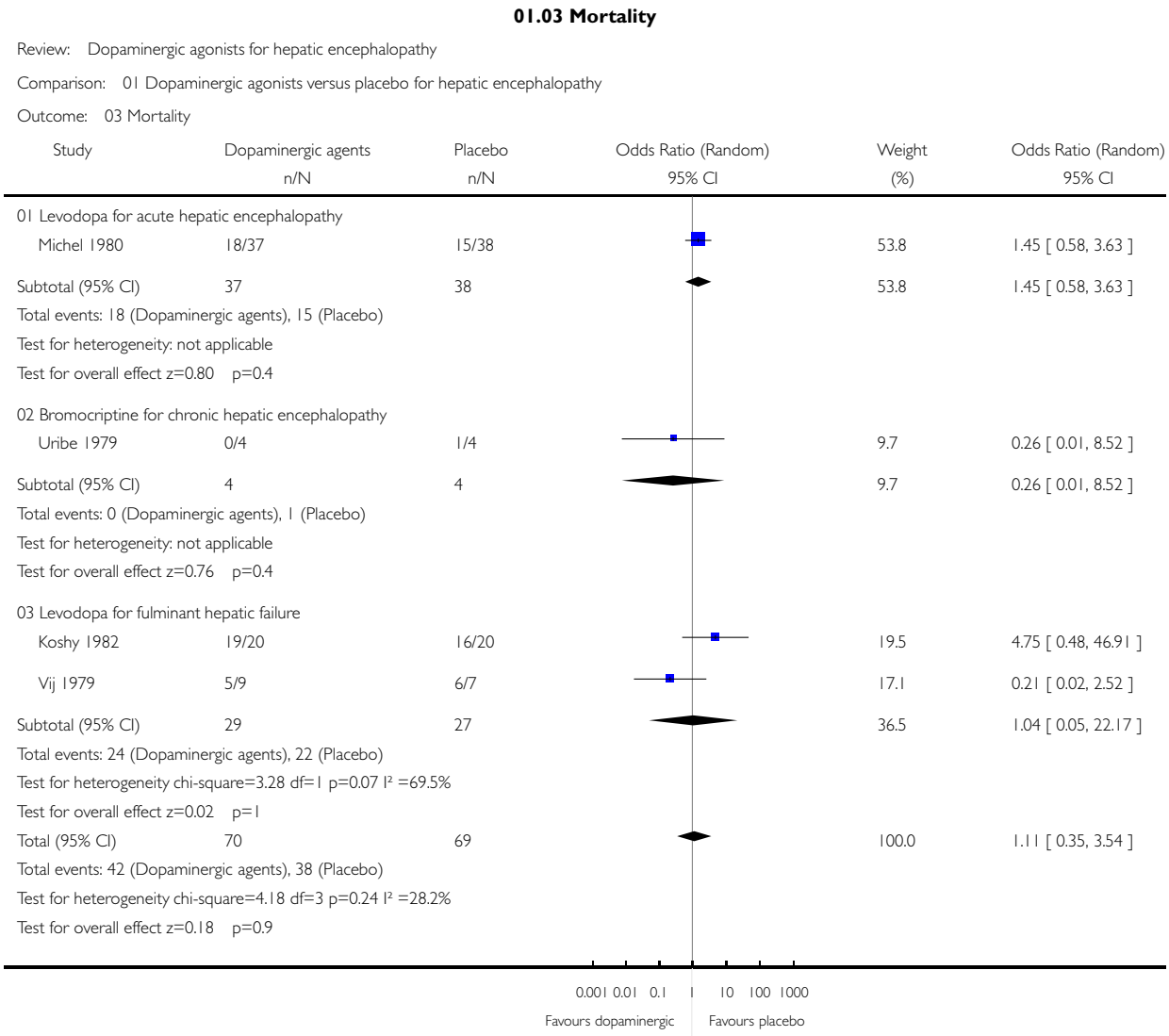


Fig. 5. Comparison 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

01.04 Adverse events

Review: Dopaminergic agonists for hepatic encephalopathy

Comparison: 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

Outcome: 04 Adverse events

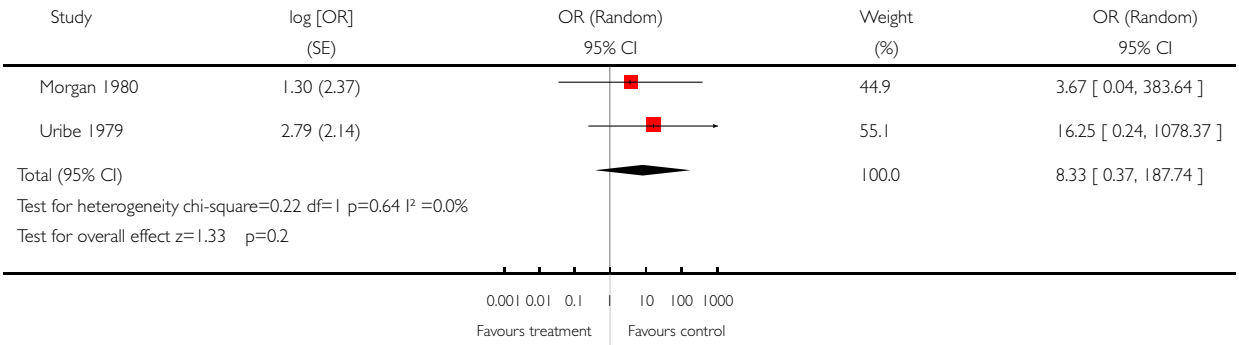


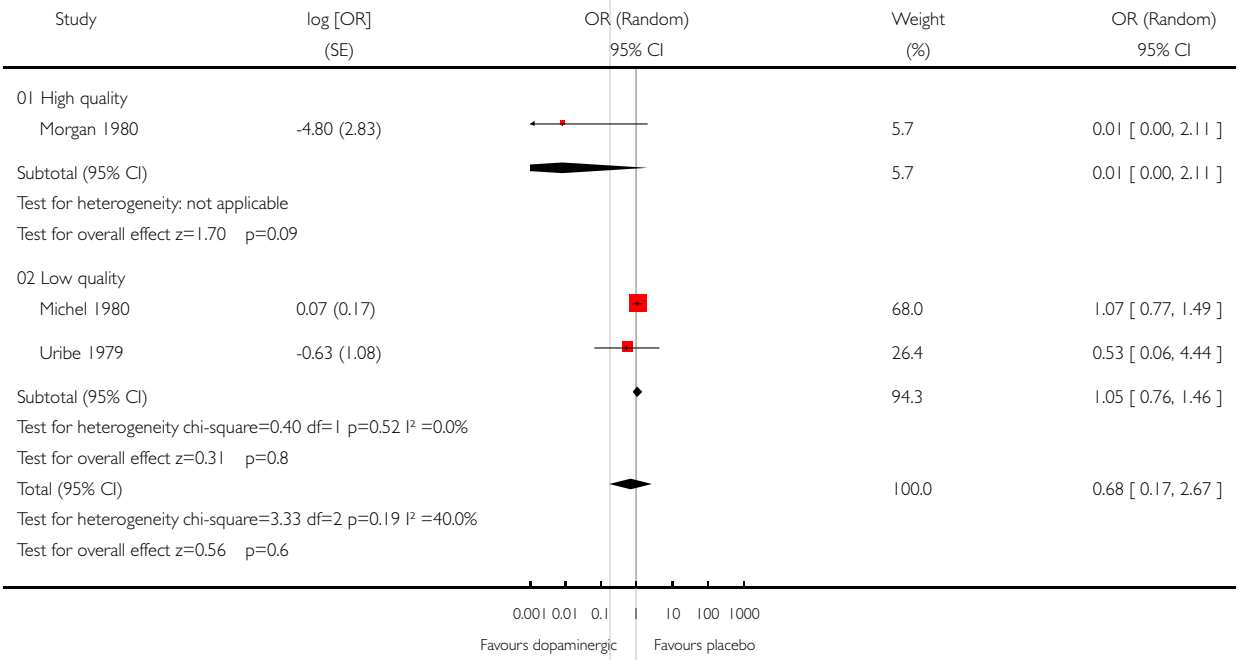
Fig. 6. Comparison 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

01.05 Sensitivity analysis - methodological quality, number of patients without improvement

Review: Dopaminergic agonists for hepatic encephalopathy

Comparison: 01 Dopaminergic agonists versus placebo for hepatic encephalopathy

Outcome: 05 Sensitivity analysis - methodological quality, number of patients without improvement



Paper 5

Artificial and Bioartificial Support Systems for Acute and Acute-on-Chronic Liver Failure

A Systematic Review

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Context Artificial and bioartificial support systems may provide a "bridge" for patients with severe liver disease to recovery or transplantation.

Objective To evaluate the effect of artificial and bioartificial support systems for acute and acute-on-chronic liver failure.

Data Sources Randomized trials on any support system vs standard medical therapy were included irrespective of publication status or language. Nonrandomized studies were included in explorative analyses. Trials were identified through electronic searches (Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Library, MEDLINE, EMBASE, and the Chinese Medical Database), bibliographies, and contact with experts. Searches were conducted of the entire databases through September 2002.

Study Selection Of 528 references identified, 12 randomized trials with 483 patients were included. Eight nonrandomized studies were included in explorative analyses.

Data Extraction Data were extracted and trial quality was assessed independently by 3 reviewers (L.L.K., J.L., B.A-N.). The primary outcome measure was all-cause mortality. Results were combined on the risk ratio (RR) scale. Random-effects models were used. Sources of heterogeneity were explored through meta-regression and stratified meta-analyses.

Data Synthesis Of the 12 trials included, 10 assessed artificial systems for acute or acute-on-chronic liver failure and 2 assessed bioartificial systems for acute liver failure. Overall, support systems had no significant effect on mortality compared with standard medical therapy (RR, 0.86; 95% confidence interval [CI], 0.65-1.12). Meta-regression indicated that the effect of support systems depended on the type of liver failure ($P=.03$). In stratified meta-analyses, support systems appeared to reduce mortality by 33% in acute-on-chronic liver failure (RR, 0.67; 95% CI, 0.51-0.90), but not in acute liver failure (RR, 0.95; 95% CI, 0.71-1.29). Compared with randomized trials, nonrandomized studies produced significantly larger estimates of intervention effects ($P=.01$).

Conclusion This review suggests that artificial support systems reduce mortality in acute-on-chronic liver failure compared with standard medical therapy. Artificial and bioartificial support systems did not appear to affect mortality in acute liver failure.

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LIVER FAILURE IS CHARACTERized by hepatic encephalopathy, jaundice, coagulopathy, and high mortality rates.[1,2] Viral hepatitis, drugs, or toxins can precipitate acute liver failure in patients without chronic liver disease.[3,4] Metabolic stress such as bleeding or infections can precipitate acute-on-chronic liver failure in patients with chronic liver disease.[5] Liver transplantation cures approximately 90% of patients with liver failure,[6,7] but there is a serious shortfall of donors and costs are considerable.[8] Furthermore, some patients may recover spontaneously without liver transplantation.[3]

The objective of artificial and bioartificial support systems is to "bridge" patients with liver failure to transplantation or recovery. Liver support must include removal of toxins, synthesis of products, and treatment of inflammation.[1] The first artificial support systems removed toxins through hemodialysis, hemofiltration, or hemoperfusion.[1,2,7] More recent systems combine hemodialysis with adsorption to charcoal or albumin (hemodiabsorption)[9,10] or use living hepatocytes, which add synthetic functions to the detoxification (bioartificial support systems).[11,12]

We performed a systematic review to evaluate the effect of artificial and bioartificial liver support systems for acute and acute-on-chronic liver failure. The primary analyses were based on randomized trials. Nonrandomized studies[13] were included in explorative analyses.[14]

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METHODS

Literature Search and Eligibility Criteria

The review was performed according to a published protocol.[15,16] Three reviewers participated in the literature searches, selection of trials, and data extraction. We included randomized trials comparing any support system vs standard medical therapy for acute or acute-on-chronic liver failure irrespective of publication status or language. Quasi-randomized and nonrandomized studies were evaluated in explorative analyses. Eligible trials were identified through Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Library, MEDLINE, EMBASE, and the Chinese Medical Database. Included terms were *liver*, *artificial*, or *liver failure,* and (*rand* or controlled*). We also screened bibliographies of relevant articles and conference proceedings and wrote experts. The searches were performed of the entire databases through September 2002.

Data Extraction and Outcome Definition

For each trial, we gathered data on the following characteristics: type of liver failure (acute or acute-on-chronic), mean age, proportion of men, type of support system, trial quality, setting, duration of follow-up, and losses to follow-up. Data were sought on all patients irrespective of compliance or follow-up. Disagreements were resolved through consensus. Primary investigators were contacted if data were incomplete.

All outcomes were assessed at maximum follow-up. The primary outcome measure was all-cause mortality. Secondary outcome measures were bridging to liver transplantation (number of patients who were too ill to receive a liver transplantation), hepatic encephalopathy (number of patients without improvement of mental state), and adverse events.[17]

Assessment of Methodological Quality and Statistical Analysis

Three reviewers (L.L.K., J.L, B.A-N.) independently assessed trial quality[18-20] by examining the allocation sequence generation, allocation concealment, and blinding of outcome assessors. The allocation sequence generation was classified as adequate if based on computer-generated random numbers, table of random numbers, or similar.[20] The allocation concealment was classified as adequate if the allocation sequence was concealed until the moment of randomization by a central independent unit, sealed envelopes, or similar.[20]

Results of individual trials were combined on the risk ratio (RR) scale. Random effects models were used. Inter-trial heterogeneity was estimated by χ^2 tests. All patients were included in the analyses irrespective of follow-up (intention-to-treat). If outcome data were missing, we used carry forward of the last-observed response. The extent to which the patient, intervention, and trial characteristics could explain heterogeneity was explored through simple random effects meta-regression. The outcome was mortality (log RR). Weights were assigned according to the estimated variance (SEs to the log RR). The following covariates were entered: type of liver failure, mean age, proportion of men, year of publication, type of support system, quality, and publication status. If the meta-regression indicated a significant association between covariates and intervention effects, RR and 95% confidence interval (CI) were calculated in stratified meta-analysis. The risk of bias was explored through statistical testing of funnel plot asymmetry.[21] Explorative meta-regression analyses including nonrandomized studies were also performed.

In a post hoc sensitivity analysis, we recalculated our primary meta-analysis without 1 trial[22] published several years before the remaining trials. We also performed a post hoc worst case scenario analysis in which patients with missing outcome data were considered as treatment failures. Analyses were performed with STATA version 6.0 (Stata Corp, College Station, Tex) and Review Manager version 4.0 (RevMan, The Cochrane Collaboration, Oxford, England). $P<.05$ was considered statistically significant.

RESULTS

Identification of Eligible Trials

After screening 528 references, we excluded 473, because they were duplicates, nonclinical, or clearly irrelevant. Of the remaining 55 references, 32 were excluded because they did not meet our inclusion criteria. Three ongoing trials could not be included because data were unavailable. Eight nonrandomized studies[23-30] were excluded from the primary analyses, but were included in explorative analyses. Twelve randomized trials on artificial or bioartificial support systems vs standard medical therapy were included in the primary analyses (TABLE 1).[9,11,12,22,31-38]

Characteristics of Patients and Interventions

The 12 trials included 483 patients with acute liver failure (n=353, 73%) or acute-on-chronic liver failure (n=130, 27%). Eleven trials reported the mean age of included patients (range, 26-53 years) and the proportion of men (range, 33%-87%). All trials were performed in intensive care units.

Ten of the included trials evaluated artificial systems (Table 1). Five trials[9,32-35] assessed the BioLogic-DT (HemoCleanse Inc, West Lafayette, Ind) system, which is based on hemodiabsorption with powdered-activate charcoal. Two trials[36,38] assessed the molecular adsorbent recirculating system, which is based on hemodiabsorption with albumin. The remaining artificial systems were whole-blood exchange,[22] charcoal hemoperfusion,[31] and plasma exchange with hemoperfusion.[37] Two trials assessed bioartificial systems based on human liver-derived tumor cells (the extracorporeal liver assist device),[11] or porcine hepatocytes (the HepatAssist device).[12] In all trials, the control groups received standard medical therapy for complications associated with severe liver failure, including electrolyte substitution, fluid substitution, antacid therapy, coagulation therapy, and *N*-acetylcysteine.

Follow-up of Included Patients

In 2 trials, the primary outcome was 30-day survival.[36,38] In the remaining trials, follow-up was estimated by the reported survival data. Overall, the median duration of follow-up was 28 days (range, 0-33 days). Of the 244 patients randomized to support systems, 7 died before treatment and 2 were withdrawn due to adverse events (Table 1). Of the 239 patients randomized to standard medical therapy, 1 patient died before treatment and 1 patient received a liver transplantation before treatment. In 1 trial,[33] data were missing on 4 patients randomized to standard medical therapy.

Methodological Quality and Publication Status of Included Trials

The allocation sequence generation was adequate in 5 trials[11,31,34,36,38] and the allocation concealment was adequate in 9 trials.[9,11,22,32-36,38] Only 1 trial reported blinded-outcome assessment.[38] Two trials were published as abstracts.[12,33] One trial was unpublished when we completed our review, but has been published as a full article.[38] The remaining trials were published as full articles.

Statistical testing of funnel plot asymmetry revealed no evidence of bias ($P=.50$). The sensitivity analyses and meta-regression did not identify significant associations between randomization ($P=.96$) or publication status ($P=.22$) and intervention effects.

Effects on Mortality

Mortality was reported in all 12 trials. The control group mortality rate was 51% (123/239). Overall, support systems did not appear to reduce mortality significantly compared with standard medical therapy (RR, 0.86; 95% CI, 0.65-1.12). The intertrial heterogeneity was significant in this analysis ($P=.04$). In meta-regression analysis, there was evidence of a significant association between the effect of support systems and the type of liver failure ($P=.03$). In a stratified meta-analysis, artificial support systems seemed to reduce mortality by 33% in acute-on-chronic liver failure (TABLE 2). Artificial and bioartificial support systems did not seem to have a significant effect on mortality in acute liver failure. In these analyses, intertrial heterogeneity was not statistically significant ($P=.43$ and $P=.15$, respectively).

The meta-regression analyses showed little evidence of an association between the effect of support systems on mortality and the following covariates: type of support system ($P=.10$), publication year ($P=.20$), mean age ($P=.06$), or proportion of men ($P=.58$).

In a post hoc sensitivity analysis, we recalculated the primary meta-analysis without 1 trial,[22] which was published in 1973. After exclusion of this trial, the effect of support systems on mortality approached statistical significance (RR, 0.78; 95% CI, 0.61-1.00). The intertrial heterogeneity was not statistically significant ($P=.20$). We also performed a post hoc worst case scenario analysis in which patients with missing outcome data were considered as treatment failures. In this analysis, support systems did not seem to have a significant effect on mortality (RR, 0.82; 95% CI, 0.62-1.08). The intertrial heterogeneity was statistically significant ($P=.02$).

Table 1. Characteristics of 12 Randomized Trials on Artificial and Bioartificial Support Systems for Liver Failure

Source	Intervention	Type of Liver Failure	Intervention Group		Control Group	
			Sample Size	Losses to Follow-up	Sample Size	Losses to Follow-up
Artificial Systems						
Redeker and Yamahori,[22] 1973	Whole-blood exchange	Acute	15	7 Died before treatment	13	None described
O'Grady et al,[31] 1988	Charcoal hemoperfusion	Acute	29	None described	33	None described
Hughes et al,[32] 1994	BioLogic-DT	Acute	5	None described	5	None described
Mazariegos et al,[33] 1997	BioLogic-DT	Acute	5	None described	5	Data missing on 4 patients
Kramer et al,[34] 1998	BioLogic-DT	Acute-on-chronic	10	None described	10	None described
Ellis et al,[35] 1999	BioLogic-DT	Acute-on-chronic	5	None described	5	None described
Mitzner et al,[36] 2001	MARS	Acute-on-chronic	8	None described	5	None described
Heemann et al,[38] 2002	MARS	Acute-on-chronic	12	None described	12	1 Died before treatment
Wilkinson et al,[9] 1998	BioLogic-DT	Acute/acute-on-chronic	6	None described	5	1 Received transplant before treatment
He et al,[37] 2000	Hemoperfusion	Acute/acute-on-chronic	64	None described	60	None described
Bioartificial Systems						
Ellis et al,[11] 1996	ELAD	Acute	12	2 Withdrawn (adverse events)	12	None described
Stevens et al,[12] 2001	HepatAssist device	Acute	73	None described	74	None described
Total			**244**		**239**	

Abbreviations: ELAD, extracorporeal liver assist device; MARS, molecular adsorbent recirculating system.

Table 2. Effect of Artificial and Bioartificial Support Systems on Mortality in Acute and Acute-on-Chronic Liver Failure*

Source	No. of Events/ No. of Patients		Weight, %	Risk Ratio (95% Confidence Interval)
	Intervention	Control		
Acute Liver Failure				
Redeker and Yamahori,[22] 1973	14/15	9/13	24.6	1.35 (0.92-1.98)
O'Grady et al,[31] 1988	19/29	20/33	24.9	1.08 (0.74-1.58)
Hughes et al,[32] 1994	4/5	2/5	5.8	2.00 (0.63-6.38)
Ellis et al,[11] 1996	4/12	5/12	7.0	0.80 (0.28-2.27)
Mazariegos et al,[33] 1997	1/5	1/5	1.4	1.00 (0.08-11.93)
Wilkinson et al,[9] 1998	0/1	1/2	1.3	0.50 (0.04-7.10)
He et al,[37] 2000	10/37	15/33	14.2	0.59 (0.31-1.14)
Stevens et al,[12] 2001	20/73	30/74	20.9	0.68 (0.42-1.08)
Total	**72/177**	**83/177**	**100**	0.95 (0.71-1.29)
Acute-on-Chronic Liver Failure				
Kramer et al,[34] 1998	4/10	4/10	7.0	1.00 (0.34-2.93)
Wilkinson et al,[9] 1998	3/5	3/3	15.7	0.60 (0.39-1.23)
Ellis et al,[35] 1999	5/5	5/5	0	NA
Mitzner et al,[36] 2001	6/8	5/5	50.4	0.75 (0.50-1.12)
He et al,[37] 2000	10/27	17/27	24.8	0.59 (0.33-1.04)
Heemann et al,[38] 2002	1/12	6/12	2.1	0.17 (0.02-1.18)
Total	**29/67**	**40/62**	**100**	0.67 (0.51-0.90)

Abbreviation: NA, not applicable.
*Because of rounding, percentages may not all total 100. Weights were assigned according to the estimated variance (SEs to the log risk ratio).

Table 3. Risk Ratios for Bridging to Transplantation and Hepatic Encephalopathy, and Type of Adverse Events in 12 Randomized Trials on Support Systems vs Standard Medical Therapy

Source	Risk Ratio (95% Confidence Interval)		Type of Adverse Events in Intervention Group†
	Bridging to Transplantation*	Hepatic Encephalopathy*	
Redeker and Yamahori,[22] 1973	Not assessed	Not assessed	None reported
O'Grady et al,[31] 1988	1.00 (0.57-1.76)	Not assessed	None reported
Hughes et al,[32] 1994	Not assessed	1.00 (0.36-2.75)	None reported
Ellis et al,[11] 1996	Not assessed	0.25 (0.03-1.92)	Bleeding, coagulopathy, hypotension, fever, hypersensitivity
Mazariegos et al,[33] 1997	0.60 (0.29-1.23)	0.60 (0.29-1.23)	Bleeding
Kramer et al,[34] 1998	0.90 (0.73-1.11)	1.00 (0.56-1.78)	Bleeding, coagulopathy, disseminated intravascular coagulation
Wilkinson et al,[9] 1998	0.62 (0.25-1.56)	0.67 (0.38-1.17)	Coagulopathy
Ellis et al,[35] 1999	Not assessed	0.50 (0.16-1.59)	None reported
He et al,[37] 2000	Not assessed	0.59 (0.38-0.90)	Bleeding, sepsis, allergic shock, hypersensitivity, arrhythmia, electrolyte imbalances
Mitzner et al,[36] 2001	Not assessed	Not assessed	Coagulopathy (low platelet count)
Stevens et al,[12] 2001	Not assessed	Not assessed	Coagulopathy, hypotension, sepsis, renal failure
Heemann et al,[38] 2002	Not assessed	0.14 (0.01-2.50)	Bleeding, coagulopathy, hypotension, fever, anemia
Overall	0.87 (0.73-1.05)	0.67 (0.52-0.86)	

*Number of patients who were too ill to receive liver transplantation.
†Reported adverse events in intervention group. The occurrence of adverse events in the control groups in individual trials was incompletely reported and no meta-analysis was performed.

Effects on Liver Transplantation and Hepatic Encephalopathy

We were able to extract data on bridging to liver transplantation from 4 trials[9,31,33,34] and hepatic encephalopathy from 8 trials.[9,11,32-35,37,38] Meta-analyses of these data indicated that support systems had no significant effect on bridging to liver transplantation (RR, 0.87; 95% CI, 0.73-1.05) but a significant positive effect on hepatic encephalopathy (RR, 0.67; 95% CI, 0.52-0.86) (TABLE 3). In these analyses, intertrial heterogeneity was not statistically significant ($P=.54$ and $P=.57$, respectively).

Adverse Events

Support systems were associated with several serious and nonserious adverse events (Table 3). The registration of adverse events associated with standard medical therapy was incomplete and we were therefore unable to perform a reliable meta-analysis of this outcome. The most important adverse event appeared to be bleeding, which was registered as serious in 3 trials[11,33,34] and nonserious in 2 trials.[37,38] Other serious adverse events included disseminated intravascular coagulation, allergic shock, fever, sepsis, hypotension, and renal failure. Eight trials reported that support systems were associated with coagulopathy because of a decrease in platelet counts or antithrombin III levels.[9,11,12,33,34,36-38] Other nonserious adverse events included hypersensitivity, electrolyte disturbances, and anemia.

Nonrandomized Studies

We performed explorative analyses in which 8 nonrandomized studies were included.[23-30] Three were case series with historical controls and assessed artificial support systems for acute liver failure.[23,25,26] Five studies were prospective with contemporary controls.[24,27-30] These studies assessed bioartificial[24] or artificial systems[27-30] and included patients with acute[24,28] or acute-on-chronic liver failure.[27,29,30]

A meta-regression analysis indicated that the estimated effect of support systems on mortality was significantly dif-

ferent in randomized trials and nonrandomized studies ($P=.01$). In randomized trials, 123 of 239 patients (51%) allocated to the control group died compared with 130 of 204 patients (64%) in studies with contemporary controls and 222 of 262 patients (85%) in studies with historical controls. Accordingly, the method of allocation (randomized or nonrandomized) was associated with control group event rates ($P=.001$). Support systems did not have a significant effect on mortality in randomized trials (RR, 0.86; 95% CI, 0.65-1.12) but appeared to reduce mortality significantly in studies with contemporary (RR, 0.72; 95% CI, 0.55-0.95) or historical controls (RR, 0.68; 95% CI, 0.58-0.80).

COMMENT

This review of 12 randomized trials compared the effect of artificial and bioartificial support systems with standard medical therapy for severe liver failure. In the primary meta-analysis, support systems did not appear to affect mortality. However, there was significant intertrial heterogeneity and meta-regression analyses indicated that the effect of support systems was associated with the type of liver failure. In a stratified meta-analysis, artificial support systems reduced mortality by 33% in acute-on-chronic liver failure. None of the identified randomized trials assessed the effect of bioartificial support systems for acute-on-chronic liver failure. Artificial and bioartificial support systems did not appear to reduce mortality in acute liver failure. However, these subgroup analyses can only be considered as hypothesis generating. Although the evidence seems promising, additional randomized trials are needed before support systems can be recommended for routine use.

The included trials were performed at specialized intensive care units. Transport to these units may be an additional hazard to patients with severe liver disease. This aspect cannot be answered by this review, but should be included in the overall assessment of intervention benefits. Another question is whether the intervention is associated with long-term benefits. Most of the included patients were followed up for about 1 month. However, the primary purpose of support systems is to bridge patients with severe liver failure to liver transplantation or recovery. Short-term follow-up is therefore important.

Mortality in severe liver failure depends on the degree of liver damage and regenerative ability. Support systems may provide a bridge during treatment of bleeding or infections, which are the most common causes of acute-on-chronic liver failure. Precipitating factors in acute liver failure include drug toxicity and viral hepatitis, which are difficult to treat. This may explain why our analyses indicated that support systems are effective in acute-on-chronic but not in acute liver failure.

We observed a positive effect of support systems on hepatic encephalopathy but not on bridging to liver transplantation. Support systems seemed to be associated with several potentially life-threatening adverse events. The most frequently reported were bleeding and infections. However, the included patients had severe liver disease, and it may be difficult to estimate whether the treatment or the underlying disease caused the adverse events. Due to incomplete reporting, we were unable to perform a reliable analysis of the occurrence of adverse events. We were also unable to assess the effect on quality-of-life and health economics. Additional evidence addressing these issues is warranted.

Limitations

This review has potential limitations. Meta-analyses are by nature observational and may therefore be affected by bias or confounding. We performed a limited number of predefined subgroup analyses. The results of these analyses should be interpreted with caution and prospective validation is needed before causal inferences can be made. Furthermore, the event rates and number of included patients indicate that our primary meta-analysis had less than 40% power of detecting a 10% reduction in mortality, possibly making our conclusions false negative.

We attempted to avoid publication bias by thorough literature searches. We found no statistically significant evidence of bias. However, the individual trials were relatively small and may therefore have generated false-negative or false-positive conclusions due to random error.[39] Only 1 trial reported preset sample size calculations.[38] In the remaining trials, we were unable to determine whether the preset sample size was reached or whether it was terminated at an arbitrary time.

Due to the nature of support systems, adequate double blinding of patients and caregivers was impossible. Blinded outcome assessment could be performed but was only used in 1 trial.[38] Improvement of hepatic encephalopathy is a soft outcome measure that may be influenced by the convictions of the assessor. Lack of blinding increases the risk of false-positive conclusions about this outcome.[18-20]

Interim analyses have a considerable risk of generating false-positive results and require very small significance levels before a trial is stopped.[40-42] One generally accepted method for assessing interim analyses[40] specifies that the significance level should be less than $P \leq .001$. One of the included trials was prematurely stopped after an interim analysis, which indicated a significant intervention benefit.[38] However, the statistical significance of the interim analysis was only 3% and the decision to terminate the trial is therefore debatable.

Nonrandomized studies may have greater external validity if patients who are willing to enter a randomized trial differ from patients who are not.[13,14] However, the question of external validity becomes irrelevant if the internal validity is questionable. If prognostic factors are unevenly distributed in the experimental and control groups, it is impossible to determine whether differences reflect the intervention or baseline prognosis.[43] We found that control group event rates were higher and intervention effects more positive in nonrandomized studies compared with randomized trials. These findings concur with previous evidence,

which indicate that nonrandomized studies have a considerable risk of generating false-positive conclusions.[43]

Implications

The present review indicates that patients with acute-on-chronic liver failure may benefit from treatment with artificial liver support systems. The evidence concerning bioartificial support systems and treatment of patients with acute liver failure was less conclusive. However, randomized trials on artificial or bioartificial support systems vs standard medical therapy for acute and acute-on-chronic liver failure still seem justified.

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Acquisition of data: Kjaergard, Liu, Als-Nielsen.
Analysis and interpretation of data: Kjaergard, Liu, Als-Nielsen, Gluud.
Drafting of the manuscript: Kjaergard.
Critical revision of the manuscript for important intellectual content: Liu, Als-Nielsen, Gluud.
Statistical expertise: Kjaergard, Liu, Als-Nielsen, Gluud.
Obtained funding: Gluud.
Study supervision: Liu, Gluud.
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