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Dopamine agents for hepatic encephalopathy (Review)

Junker AE, Als-Nielsen B, Gluud C, Gluud LL

Junker AE, Als-Nielsen B, Gluud C, Gluud LL.
Dopamine agents for hepatic encephalopathy.
Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD003047.
DOI: 10.1002/14651858.CD003047.pub3.

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[Intervention Review]

Dopamine agents for hepatic encephalopathy

Anders Ellekær Junker[1], Bodil Als-Nielsen[2], Christian Gluud[3], Lise Lotte Gluud[4]

[1]Department of Medicine F, Gentofte Hospital, Hellerup, Denmark. [2]Department of Paediatric Haematology/Oncology (5054), The Child and Youth Clinic, Copenhagen, Denmark. [3]The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [4]Gastro Unit, Medical Division, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

Contact: Anders Ellekær Junker, Department of Medicine F, Gentofte Hospital, Niels Andersens Vej 65, Hellerup, 2900, Denmark. andjunker@dadlnet.dk.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 2, 2014.

Citation: Junker AE, Als-Nielsen B, Gluud C, Gluud LL. Dopamine agents for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No.: CD003047. DOI: 10.1002/14651858.CD003047.pub3.

ABSTRACT

Background

Patients with hepatic encephalopathy may present with extrapyramidal symptoms and changes in basal ganglia. These changes are similar to those seen in patients with Parkinson's disease. Dopamine agents (such as bromocriptine and levodopa, used for patients with Parkinson's disease) have therefore been assessed as a potential treatment for patients with hepatic encephalopathy.

Objectives

To evaluate the beneficial and harmful effects of dopamine agents versus placebo or no intervention for patients with hepatic encephalopathy.

Search methods

Trials were identified through the Cochrane Hepato-Biliary Group Controlled Trials Register (January 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 12 of 12, 2013), MEDLINE (1946 to January 2014), EMBASE (1974 to January 2014), and Science Citation Index-Expanded (1900 to January 2014). Manual searches in reference lists, conference proceedings, and online trial registers were also performed.

Selection criteria

Randomised trials were included, irrespective of publication status or language. The primary analyses included data from randomised trials using a parallel-group design or the first period of cross-over trials. Paired data from cross-over trials were included in sensitivity analyses.

Data collection and analysis

Three review authors extracted data independently. Random-effects meta-analyses were performed as the result of an expected clinical heterogeneity. Fixed-effect meta-analyses, meta-regression analyses, subgroup analyses, and sensitivity analyses were performed to evaluate sources of heterogeneity and bias (systematic errors). Trial sequential analysis was used to control the risk of play of chance (random errors).

Main results

Five trials that randomly assigned 144 participants with overt hepatic encephalopathy that were published during 1979 to 1982 were included. Three trials assessed levodopa, and two trials assessed bromocriptine. The mean daily dose was 4 grams for levodopa and 15 grams for bromocriptine. The median duration of treatment was 14 days (range seven to 56 days). None of the trials followed participants

after the end of treatment. Only one trial reported adequate bias control; the remaining four trials were considered to have high risk of bias. Random-effects model meta-analyses showed that dopamine agents had no beneficial or detrimental effect on hepatic encephalopathy in the primary analyses (15/80 (19%) versus 14/80 (18%); odds ratio (OR) 2.99, 95% confidence interval (CI) 0.09 to 100.55; two trials) or when paired data from cross-over trials were included (OR 1.04, 95% CI 0.75 to 1.43). Clear evidence of intertrial heterogeneity was identified both in the primary analysis (I^2 = 65%) and when paired data from cross-over trials were included (I^2 = 40%).

Dopamine agents had no beneficial or harmful effect on mortality (42/144 (29%) versus 38/144 (26%); OR 1.11, 95% CI 0.35 to 3.54; five trials). Trial sequential analyses demonstrated that we lacked information to refute or recommend the interventions for all outcomes. Dopamine agonists did not seem to increase the risk of adverse events.

Authors' conclusions

This review found no evidence to recommend or refute the use of dopamine agents for hepatic encephalopathy. More randomised placebo-controlled clinical trials without risks of systematic errors and risks of random errors seem necessary to permit firm decisions on dopamine agents for patients with hepatic encephalopathy.

PLAIN LANGUAGE SUMMARY

Dopamine agents for hepatic encephalopathy

Hepatic encephalopathy is a serious complication of severe liver disease. The disease is often fluctuating with a wide spectrum of symptoms ranging from minor, not readily discernible signs to deep coma. Symptoms often develop in connection to stress related to infection, dehydration, obstipation, or gastrointestinal bleeding. The exact underlying mechanisms behind the disease development are not known. Experimental studies suggest that the mental changes seen in hepatic encephalopathy reflect changes in neurotransmitters in the brain.

Dopamine plays a major role in neurotransmission. Several nervous system diseases including Parkinson's disease are caused by a dysfunction in the dopamine system. Some patients with hepatic encephalopathy have symptoms that are similar to those seen in patients with Parkinson's disease (slow cerebration; stiffness of movements; tremor). For patients with Parkinson's disease, the drugs known as dopamine agents (drugs that mimic the effect of the neurotransmitter dopamine) clearly alleviate symptoms. These drugs have also been assessed for patients with hepatic encephalopathy.

We performed the present systematic review to determine the beneficial and harmful effects of dopamine agents for patients with hepatic encephalopathy. Our analyses included five small trials published in 1982 or earlier. All trials but one had high risks of bias (i.e., risks of systematic errors or risks of overestimation of beneficial effects or risks of underestimation of harmful effects). Only 144 patients were included in the five trials, and accordingly risks of random errors (i.e., play of chance) are present. Our analyses showed no significant differences regarding symptoms of hepatic encephalopathy or mortality in patients treated with dopamine agents compared with patients who received an inactive placebo or no intervention. The number of patients with adverse events seemed comparable in the two intervention groups. Based on the available evidence, we conclude that no evidence can be found to recommend or refute the use of dopamine agents for hepatic encephalopathy. More randomised placebo-controlled clinical trials without risks of systematic errors and risks of random errors seem necessary to obtain firm evidence on dopamine agents for patients with hepatic encephalopathy.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Dopamine agonists for hepatic encephalopathy

Dopamine agonists versus placebo or no intervention for hepatic encephalopathy

Patient or population: patients with hepatic encephalopathy.
Settings: hospitalised patients.
Intervention: dopamine agonists versus placebo or no intervention.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (placebo or no intervention)	Dopamine agonists				
Mortality Follow-up: mean one month	**Study population**		**OR 1.11** (0.35 to 3.54)	144 (five studies)	⊕⊕⊖⊖ **low** [1,2,3]	
	535 per 1000	**561 per 1000** (287 to 803)				
	Moderate					
	395 per 1000	**420 per 1000** (186 to 698)				
Hepatic encephalopathy Follow-up: mean one month	**Study population**		**OR 2.99** (0.09 to 100.55)	80 (two studies)	⊕⊕⊖⊖ **low** [1,2,3]	
	350 per 1000	**617 per 1000** (46 to 982)				
	Moderate					
	184 per 1000	**403 per 1000** (20 to 958)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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[1]The randomisation methods were classed as adequate in two trials, and three trials were double-blind.
[2]The sample size was small, and the statistical power of included trials was weak.
[3]Because of the small number of trials, tests for publication bias were of limited value.

BACKGROUND

Description of the condition

Hepatic encephalopathy is a complex neuropsychiatric syndrome seen in severe liver failure (Gitlin 1996; Ferenci 2002). Symptoms range from minor neuropsychiatric changes to deep coma (Conn 1979). Hepatic encephalopathy may be clinically overt or may consist of mild neurocognitive impairments, which have been identified in a substantial percentage of patients with liver disease (Randolph 2009). The course of the disease may be episodic, with recurrent symptoms, or chronic, with more stable symptoms (Bajaj 2011). The exact underlying pathophysiology is not known. Experimental studies suggest that symptoms develop as the result of accumulation of toxic agents that have not been metabolised by the liver (Gitlin 1996). Other potential mechanisms include the generation of false neurotransmitters and an abnormal interaction between astrocytes and other cellular elements with cerebral oedema and alterations in glioneural communication (Haussinger 2000; Cordoba 2001).

Description of the intervention

Many patients with hepatic encephalopathy present with extrapyramidal symptoms and have changes in the basal ganglia, as detected by magnetic resonance imaging and proton spectroscopy (Spahr 2000). These symptoms are comparable with those seen in Parkinson's disease and suggest an impairment of dopamine neurotransmission (Blei 1999; Jover 2003). Patients with Parkinson's disease are less likely to experience dyskinesia and dystonia when treated with levodopa (Stowe 2008). Uncontrolled trials suggest that levodopa or bromocriptine could be beneficial in the treatment of patients with hepatic encephalopathy (Parkes 1970; Jorge 1973). The effects of dopamine agents have also been assessed in randomised clinical trials (Uribe 1979; Michel 1980; Morgan 1980), and previous guidelines suggested that the intervention may be considered in patients with chronic hepatic encephalopathy (Blei 1999; Lizardi-Cervera 2003).

Why it is important to do this review

We have previously published a systematic review on dopamine agents for hepatic encephalopathy (Als-Nielsen 2004a). The results of this review were inconclusive. We have been unable to identify any further meta-analyses or systematic reviews on the topic. To determine the strengths and weaknesses of the current evidence, we have updated our previous review (Als-Nielsen 2004a).

OBJECTIVES

To evaluate the beneficial and harmful effects of dopamine agents versus placebo or no intervention for patients with hepatic encephalopathy.

METHODS

Criteria for considering studies for this review

Types of studies

This review included all randomised trials, regardless of publication status, language, or blinding. Unpublished trials were included if the methodology and the data were available in written form. We planned to include observational studies reporting harms, but we identified no observational studies reporting relevant data.

Types of participants

Patients with hepatic encephalopathy were included, irrespective of the aetiology of the underlying liver disease. The diagnostic criteria could include psychometric tests, clinical scoring systems (such as the West-Haven criteria), electroencephalography (Guerit 2009), or biochemical findings (including ammonia levels). Based on the diagnostic criteria used in the included trials, participants were classified as having overt or minimal hepatic encephalopathy, and the latter was classified further as recurrent or chronic.

Types of interventions

The intervention comparisons assessed were dopamine agents (e.g., levodopa, bromocriptine) versus placebo or no intervention. Studies were included irrespective of the dose or duration of therapy.

Types of outcome measures

Primary outcomes

- Mortality (all-cause).
- All cause non-fatal serious adverse events.
- Morbidity. This outcome measure was assessed on the basis of the number of participants who showed no improvement in manifestations of hepatic encephalopathy as defined by the authors of included trials.

Secondary outcomes

- All-cause non-serious adverse events (number and type) (ICH-GCP 1997).
- Qualitiy of life.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Science Citation Index-Expanded (Royle 2003). Search strategies with time spans of the searches are given in Appendix 1.

Searching other resources

Reference lists in relevant articles and conference proceedings were scanned for additional trials not identified in the electronic searches. We wrote to authors of identified trials and pharmaceutical companies to enquire about additional trials. Ongoing and completed trials were also identified through searches in the World Health Organization Trial Search Portal (www.who.int/trialsearch/).

Data collection and analysis

Selection of studies

All review authors participated in the selection of trials. AEJ listed the potentially eligible trials. Subsequently, trials that fulfilled all inclusion criteria were identified. Excluded trials were listed along with the reasons for exclusion.

Data extraction and management

Three review authors (AEJ, BA-N, and LLG) extracted data independently. All disagreements were resolved through discussion before analyses.

We extracted data on the design of the trial (country of origin, parallel or cross-over design, and bias control), participant characteristics (aetiology of underlying liver diseases and type of hepatic encephalopathy, mean age, proportion of men), and the intervention regimen assessed (type, dose, and duration of therapy).

Assessment of risk of bias in included studies

We assessed the risk of bias in the trials independently in accordance with the instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2013). Because of the risk of overestimation of intervention effects in randomised trials with high risk of bias (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savovic 2012, Savovic 2012a), we assessed the influence of risk of bias on trial results using the following domains.

Allocation sequence generation

- Low risk of bias: Sequence generation was achieved by using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Uncertain risk of bias: The method of sequence generation was not specified.
- High risk of bias: The sequence generation method was not random.

Allocation concealment

- Low risk of bias: The participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g., if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Uncertain risk of bias: The method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: The allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants, personnel, and outcome assessors

- Low risk of bias: Blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: Information was insufficient to permit assessment of whether blinding was likely to induce bias on the results.
- High risk of bias: No blinding or incomplete blinding was performed, and assessment of outcomes was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: Missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, had been employed to handle missing data.
- Uncertain risk of bias: Information was insufficient to permit assessment of whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: The results were likely to be biased as the result of missing data.

Selective outcome reporting

- Low risk of bias: All outcomes were predefined and reported, or all clinically relevant and reasonably expected outcomes were reported. The trial was registered on the www.clinicaltrials.gov web site or on a similar register, or the protocol was published.
- Uncertain risk of bias: It was unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported.
- High risk of bias: One or more clinically relevant and reasonably expected outcomes were not reported, and data on these outcomes were likely to have been recorded.

Other bias

- Low risk of bias: The trial appears to be free of other components that could put it at risk of bias.
- Uncertain risk of bias: The trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: Other factors in the trial could put it at risk of bias (e.g., for-profit involvement, authors conducting trials on the same topic).

Trials with unclear or high risk of bias methodology in one or more of the above domains were considered trials with high risk of bias. The remaining were considered trials with low risk of bias.

Measures of treatment effect

All outcome measures were dichotomised and were expressed using odds ratios (ORs) with 95% confidence intervals (CIs).

Unit of analysis issues

The primary analyses included data from trials using a parallel-group design and from the first treatment period of cross-over trials. Additional analyses were performed that included paired data from the cross-over trials (Becker 1993; Elbourne 2002).

Dealing with missing data

Data on all participants randomly assigned were sought to allow intention-to-treat analyses that included participants irrespective of compliance or follow-up. For participants with missing data, carry-forward of the last observed response was used. We originally planned to analyse the influence of missing data using imputation (Higgins 2008). We planned to impute missing values as failures, successes, same as control group, same as experimental group, and same as own group (Higgins 2008). We did not perform these analyses because no losses to follow-up were described.

Assessment of heterogeneity

Intertrial heterogeneity was assessed on the basis of I^2 values.

Assessment of reporting biases

We planned to evaluate the risk of reporting bias by comparing trial protocols and published reports. Furthermore, reporting biases were assessed on the basis of the extent to which clinically relevant outcome measures (hepatic encephalopathy, mortality, and adverse events) were reported.

Data synthesis

Analyses were performed in Review Manager 5 (RevMan 2012) and in STATA 12 (STATA 12). Primary meta-analyses were performed by using random-effects models because of anticipated variability between trials regarding participants and interventions.

Subgroup analysis and investigation of heterogeneity

Originally, we planned to perform several subgroup analyses to assess sources of intertrial heterogeneity (bias control, participant characteristics, and intervention regimens). However, because of the limited number of trials in the meta-analyses of the primary outcomes, we were able to perform these subgroup analyses only for the outcome measure of mortality. Likewise, regression analyses (Egger's test) that were planned to estimate the risk of publication bias and other biases (small-study effects) were performed only for the outcome measure of mortality.

Trial sequential analysis

We performed trial sequential analysis (CTU 2011; Thorlund 2011) to control risks of random errors due to sparse data and repetitive testing of cumulative data (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010). To minimise the risk of random error, we calculated the required information size, defined as the required sample size necessary to detect or reject intervention effects after adjusting for diversity (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010). The information size was calculated on the basis of a risk ratio (RR) reduction of 20% or the results of included trials with a low risk of bias (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010). We presented the results of the analysis in a graph. with individual trials added on the basis of their year of publication. If more than one trial was published in a year, trials were added alphabetically according to the first author's family name. The results of the trials were presented as a cumulative Z-curve. The trial sequential monitoring boundaries were constructed and the diversity-adjusted required information size calculated with a type 1 error of 5% and a type 2 error of 20%. The results were displayed as a graph with the cumulative meta-analysis results entered. The trial sequential analysis shows firm evidence of intervention effects (or no intervention effects) if the cumulative Z-curve crosses the monitoring boundaries; it also shows that additional trials may be needed if the boundaries are not crossed.

Sensitivity analysis

The robustness of the results was assessed by repeating the meta-analyses using a fixed-effect model. No additional sensitivity analyses were performed because of the limited number of trials identified.

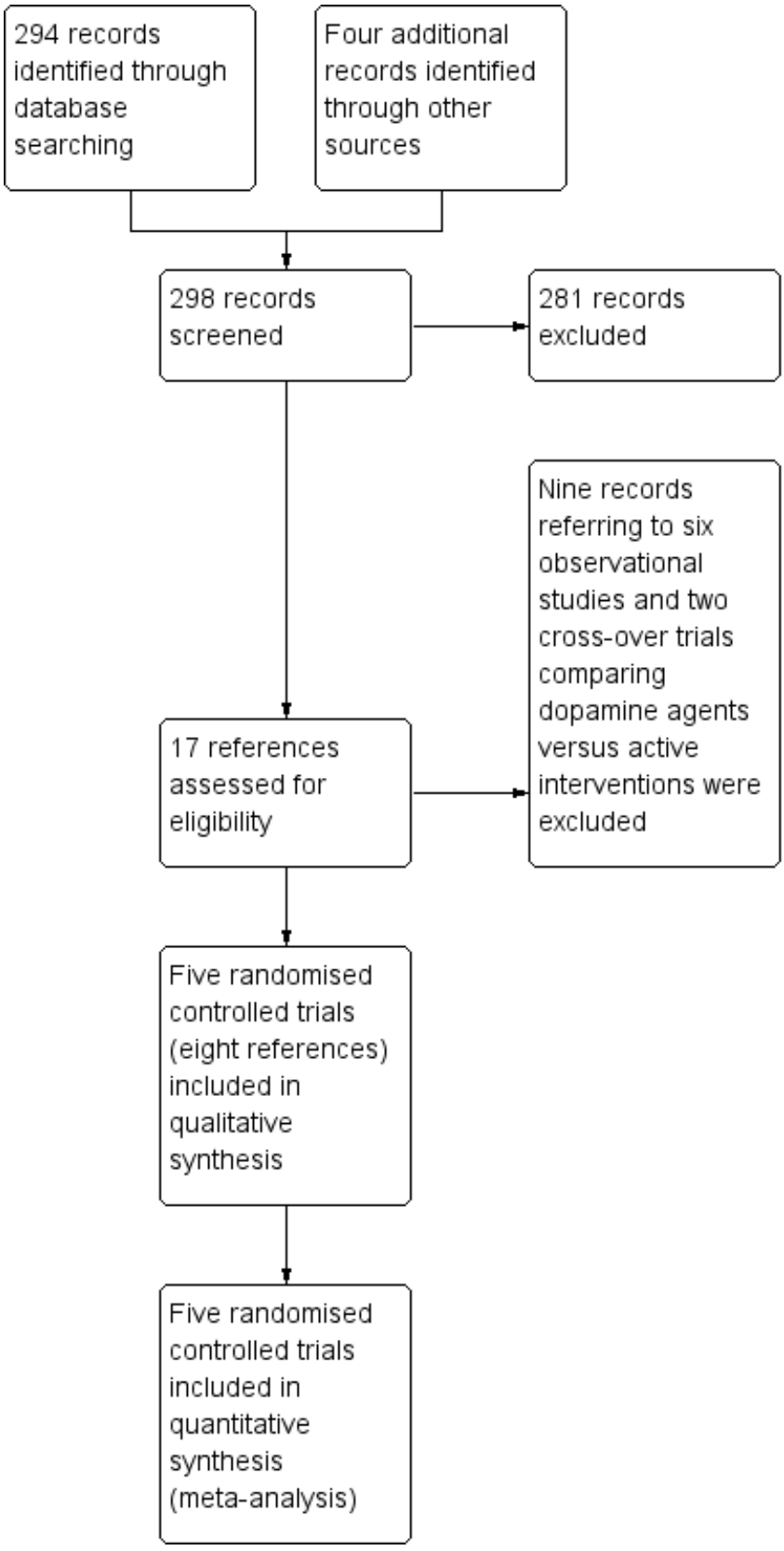
RESULTS

Description of studies

Results of the search

In total, 294 references were identified through the literature searches (Appendix 1). After duplicates and clearly irrelevant references (references to papers that did not describe trials of dopaminergic agents for participants with hepatic encephalopathy) were excluded, 17 references were retrieved for further assessment (Figure 1). Of these, eight references referred to five randomised trials that were eligible for inclusion (Uribe 1979; Vij 1979; Michel 1980; Morgan 1980; Koshy 1982). Through correspondence with the authors of two trials (Uribe 1979; Morgan 1980), additional information was obtained on trial results and methods. For the remaining trials, data were gathered from published reports.

Figure 1. Figure 1. Study flow diagram.



Included studies

All of the included trials were described in at least one full-paper article published from 1979 to 1982. Three trials used a parallel-group design (Vij 1979; Michel 1980; Koshy 1982), and two trials used a cross-over design (Uribe 1979; Morgan 1980).

In total, 144 participants with overt hepatic encephalopathy were included. Three trials (66 participants in the treatment group versus 65 participants in the control group) assessed acute episodes of hepatic encephalopathy (Vij 1979; Michel 1980; Koshy 1982). Two trials (seven participants in the treatment group versus six participants in the control group) assessed chronic hepatic encephalopathy (Uribe 1979; Morgan 1980). Two trials included participants with acute fulminant liver failure due to viral hepatitis (Vij 1979; Koshy 1982). Three trials included participants with cirrhosis (Uribe 1979; Michel 1980; Morgan 1980). The proportion of participants with alcoholic liver disease ranged from 0 to 80%. The proportion of participants with viral hepatitis ranged from 0 to 100%, and mean age ranged from 32 years to 57 years.

Three trials assessed levodopa (Vij 1979; Michel 1980; Koshy 1982), and two trials assessed bromocriptine (Uribe 1979; Morgan 1980). The mean daily dose was 4 grams for levodopa and 15 grams for bromocriptine. The median duration of treatment was 14 days (range seven to 56 days). None of the trials followed participants after the end of treatment. None of the included trials assessed health economics.

Excluded studies

Nine references to eight trials were excluded because they turned out not to be randomised or referred to cross-over trials that compared dopamine agents versus interventions for hepatic encephalopathy considered potentially active (Characteristics of included studies).

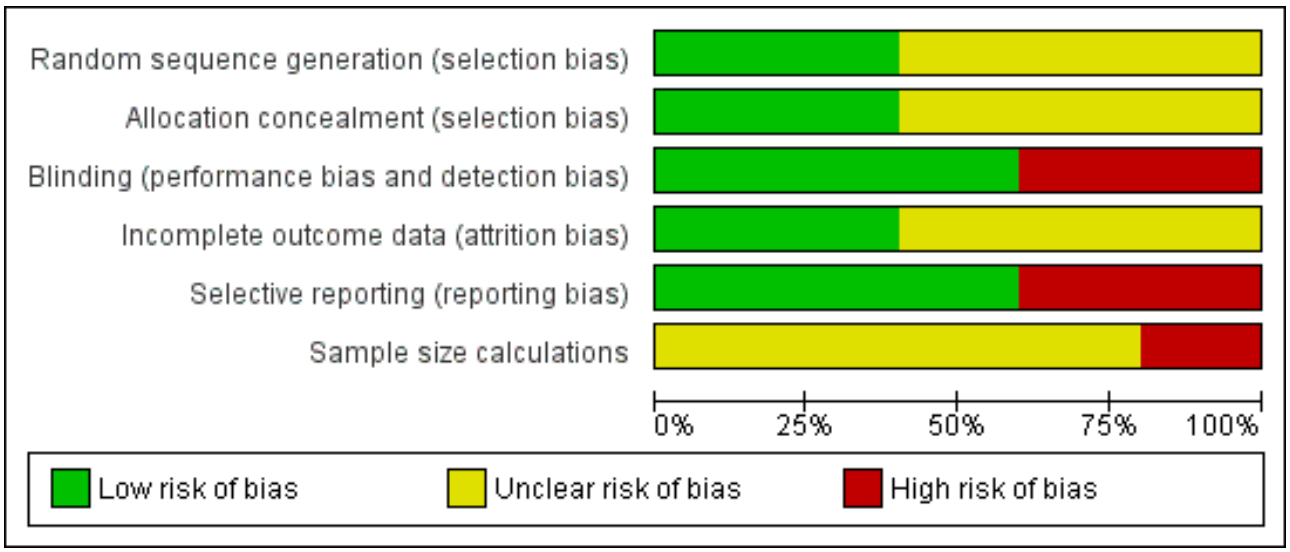
Risk of bias in included studies

All trials had a high risk of bias in the assessment of one or more than one of the bias risk domains.

Allocation

Randomisation methods (allocation sequence generation and allocation concealment) were classed as adequate in two trials (Uribe 1979; Morgan 1980) and unclear in the remaining trials (Figure 2).

Figure 2. Figure 2. Risk of bias graph: review authors' judgements about all risk of bias items presented as percentages across all included studies.



Blinding

Three trials were blinded using a placebo (Uribe 1979; Michel 1980; Morgan 1980). No blinding was described in the remaining trials.

Incomplete outcome data

Two trials accounted for all participants with missing outcome data (Uribe 1979; Morgan 1980). In the remaining three trials, no dropouts or withdrawals were described, giving the impression that no losses to follow-up occurred, although this was not specifically stated.

Selective reporting

We were able to extract data on hepatic encephalopathy from only three trials (Uribe 1979; Michel 1980; Morgan 1980).

Other potential sources of bias

No sample size calculations were reported. None of the included trials received industry funding.

Effects of interventions

See: **Summary of findings for the main comparison** Dopamine agonists for hepatic encephalopathy

Mortality

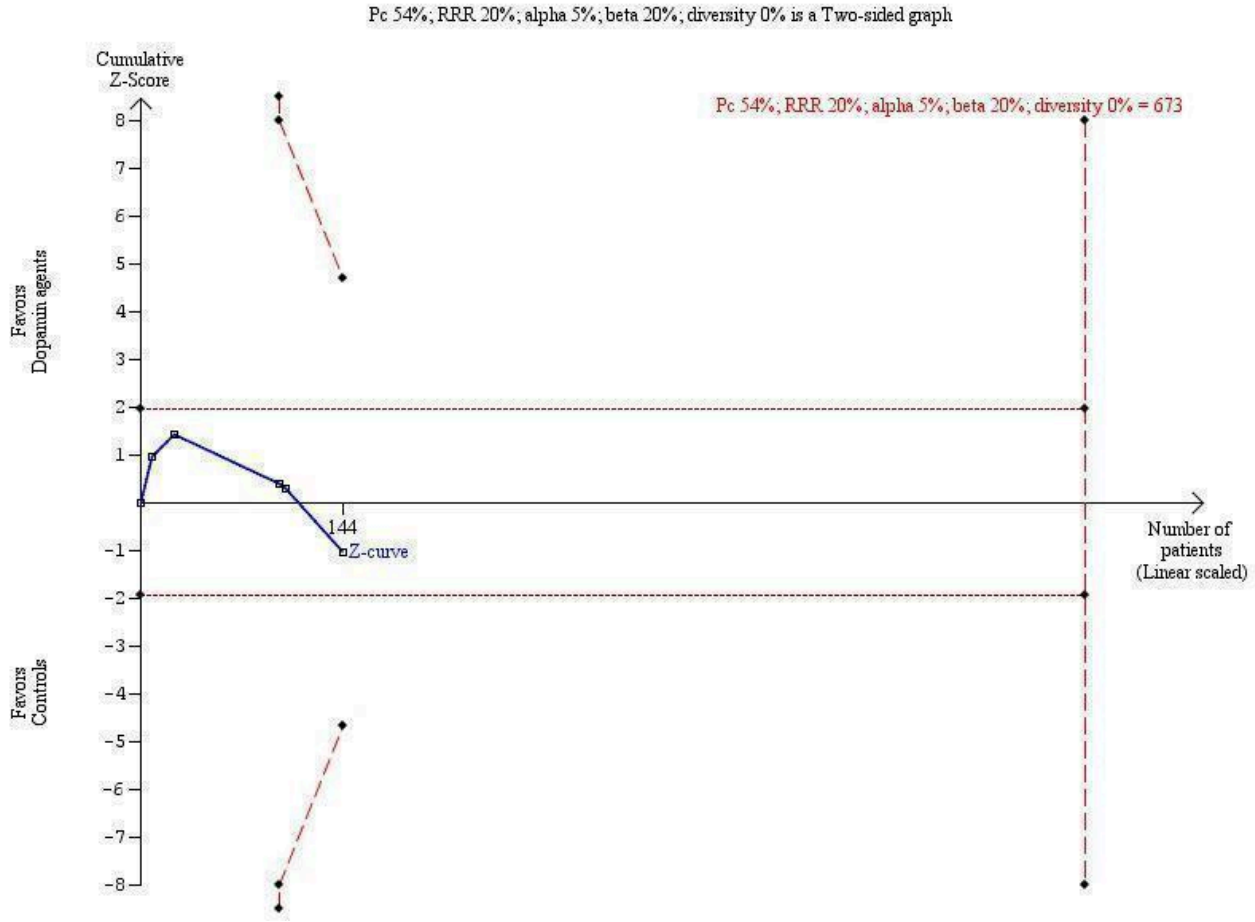
Random-effects meta-analyses found no difference in mortality between participants randomly assigned to dopamine agents versus controls (OR 1.11, 95% CI 0.34 to 3.54; Analysis 1.1). Little intertrial heterogeneity was noted (I^2 = 28%). The result was

confirmed in a fixed-effect meta-analysis (OR 1.24, 95% CI 0.59 to 2.59). No evidence of small-study effects was identified in regression analysis (Egger's test P value 0.35). In subgroup analyses, no clear differences were seen between trials on participants with acute episodes compared with chronic hepatic encephalopathy (Analysis 1.2) or participants with fulminant liver failure or cirrhosis (Analysis 1.3), trials on levodopa or bromocriptine (Analysis 1.4), trials with a low or unclear risk of bias (Analysis 1.5), or trials using a parallel or cross-over design (Analysis 1.6).

The trial sequential analysis graph showed that the cumulative Z-curve does not cross the monitoring boundary (Figure 3). The analysis showed a diversity-adjusted required information size of 673 participants (the number of participants needed to reach firm evidence of an intervention effect of 20% risk ratio reduction). The number of participants included corresponds to only 21% of the diversity-adjusted required information size. Accordingly, we lack evidence to recommend or refute dopamine agents for hepatic encephalopathy.

Figure 3. Trial sequential analysis of dopamine agents versus placebo or no intervention in participants with hepatic encephalopathy.

The outcome measure is mortality. The analysis was performed with an event rate of 54% (Pc) in the control group, a risk ratio (RR) reduction of 20%, alpha 5%, beta 20%, and diversity 0%. The cumulative Z-curve does not cross the naive 5% statistical boundaries (dotted horizontal lines) or the trial sequential boundaries for benefits or harms (inward sloping etched lines). The results show that the diversity-adjusted required information size was 673 participants, corresponding to 21% of the total sample size in the included trials. The programme did not even draw futility boundaries. Accordingly, the meta-analysis does not recommend or refute an intervention effect; data are simply too few.



Hepatic encephalopathy

The primary random-effects meta-analyses showed no significant effects of dopamine agents on hepatic encephalopathy compared with placebo or no intervention when data from parallel-group trials were analysed (OR 0.33, 95% CI 0.01 to 11.25; Analysis 1.7) or when paired data from the cross-over trial reporting this outcome measure were included (OR 0.68, 95% CI 0.17 to 2.67; Analysis 1.8). The results were confirmed by fixed-effect meta-analyses including data from parallel-group trials (OR 1.08, 95% CI 0.45 to 2.62), but also when paired data from the two cross-over trials reporting this outcome measure were included (OR 1.04, 95% CI 0.75 to 1.43).

Adverse events

We were able to retrieve data on adverse events only from the two cross-over trials (Uribe 1979; Morgan 1980). In total, seven of 13 participants experienced non-serious adverse events during treatment with dopamine agents. No adverse events were reported during control periods. No clear difference was observed between intervention and control groups (Analysis 1.9). No serious adverse events were registered. Adverse events included hypomania (n = 1), hallucinations and headache (n = 1), constipation (n = 3), and nausea and vomiting (n = 2).

Quality of life

None of the included trials reported data on quality of life.

DISCUSSION

Summary of main results

Patients with cirrhosis may present with extrapyramidal symptoms similar to those seen in Parkinson's disease (Jover 2003). Further similarities between participants with hepatic encephalopathy and participants with Parkinson's disease include alterations in the basal ganglia (Spahr 2000). In theory, dopamine agents that are effective in Parkinson's disease could alleviate manifestations of hepatic encephalopathy. However, the present systematic review found no evidence to recommend or refute the use of dopamine agents for patients with hepatic encephalopathy. The available evidence includes only a limited number of small trials published before 1983. No clear effects were identified for any of the outcome measures assessed. Additional analyses found no specific subgroups that indicated potential effects when the results of included trials were separated on the basis of the type of hepatic encephalopathy at inclusion, the type of underlying liver disease, or the intervention assessed. The dose and duration of the interventions assessed were similar across trials. Data from participants with Parkinson's disease (Miyasaki 2002) show that the dose of both levodopa and bromocriptine and the duration of the intervention regimens assessed in included trials should be sufficiently high to detect a clinical response. The combined evidence is not promising. However, the statistical power is low, and evidence is insufficient to support or refute beneficial or harmful effects of the interventions assessed.

Overall completeness and applicability of evidence

To ensure completeness of the evidence, we performed extensive literature searches. Our regression analyses showed no clear evidence of publication bias or other small-study effects. Still, the regression analysis was not sensitive because of the limited number of trials.

The main problem with the included trials is the fact that a number of potentially effective interventions for patients with decompensated liver disease have been identified after the trials were completed. These interventions include treatments for hepatic encephalopathy (Bass 2010), bleeding oesophageal varices (Abraldes 2007), and spontaneous bacterial peritonitis (Wiest 2012). Likewise, the diagnostic assessment and nomenclature for hepatic encephalopathy have been updated (Bajaj 2011). Accordingly, extrapolation of results from the present review to current clinical practice is of limited value.

Quality of the evidence

Adequate internal validity depends on the control of bias and random errors. Because three trials had unclear randomisation (Michel 1980; Morgan 1980; Koshy 1982) and consequently an unclear control of selection bias, the internal validity of their results and of the results of our meta-analyses can be questioned. The use of a cross-over design as applied in two of the included trials (Uribe 1979; Morgan 1980) is also debatable. Even chronic hepatic encephalopathy may have a fluctuating course (Basile 1991); therefore, manifestations of hepatic encephalopathy may change during the course of the trial, irrespective of the interventions assessed. The underlying condition and the ability to respond to treatment may not remain stable from the first to the second treatment period. We therefore used only data from the first study period of the cross-over trials in our primary analyses. Unfortunately, these data were available for only one trial (Morgan 1980). The sensitivity analysis on paired data did not change our overall result.

Potential biases in the review process

Identification and selection of trials are essential to the assessment of bias in the review process. To limit bias in the selection process, we included trials irrespective of language or publication status. We also chose to include trials regardless of the dose or duration of the interventions assessed. This led to a relatively heterogeneous group of trials. We did, however, choose to exclude trials with an active comparison group. This choice was made on the basis of lack of evidence supporting several of the interventions assessed for patients with hepatic encephalopathy. The strategy resulted in the exclusion of two small, low-quality, cross-over trials on chronic hepatic encephalopathy (Messner 1982; Uribe 1983). The control groups in these trials received lactulose or neomycin, which could affect the course of hepatic encephalopathy. The total number of participants randomly assigned in these two trials was only 15, and this limits the value of these results.

Agreements and disagreements with other studies or reviews

At present, dopamine agents are not recommended for patients with hepatic encephalopathy. Previous guidelines state that bromocriptine may be considered for patients with chronic hepatic encephalopathy that is unresponsive to other interventions (Blei 1999). In agreement with more recent recommendations (Phongsamran 2010), the present review contradicts these recommendations, suggesting that no evidence is available to support the use of dopamine agents for chronic hepatic encephalopathy.

AUTHORS' CONCLUSIONS

Implications for practice

This review does not provide evidence to recommend or refute the use of dopamine agents for patients with hepatic encephalopathy.

Implications for research

However, we cannot exclude the possibility that dopamine agents may have beneficial effects that were overlooked because of the limited statistical power of the included trials. On the other hand, other interventions for hepatic encephalopathy (such as

non-absorbable disaccharides, branched chain amino acids, and antibiotics) appear potentially more promising than dopamine agents (Als-Nielsen 2004a; Bass 2010; Les 2011). The value of additional trials on dopamine agents is questionable. Should anyone wish to conduct further trials, we recommend that the dopamine agent used should be tested against placebo in parallel-group superiority trials conducted according to the SPIRIT guidelines (SPIRIT 2013; SPIRIT 2013a) and reported according to the CONSORT guidelines (www.consort-statement.org).

ACKNOWLEDGEMENTS

We thank Marsha Morgan and Misael Uribe for providing additional information on their trials, and Sarah Klingenberg for performing the electronic literature searches.

Peer reviewers: FG Romeiro, Brazil; Diego Sánchez-Munoz, Spain.
Contact editor: Goran Bjelakovic, Serbia.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Koshy 1982

Methods	• Parallel-group trial.
Participants	• Type of hepatic encephalopathy: acute episodes associated with fulminant liver failure. • Type of underlying liver disease: fulminant liver failure due to viral hepatitis (100%). • Mean age: not reported. • Proportion of men: not reported.
Interventions	• Dopamine agent: levodopa 4 grams/d. • Control: no intervention. • Treatment duration: not reported.
Outcomes	• Mortality.
Notes	• Health economics: not assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.

Koshy 1982 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not described.
Selective reporting (reporting bias)	High risk	Hepatic encephalopathy not reported.
Sample size calculations	High risk	No.

Michel 1980

Methods	• Parallel-group trial.
Participants	• Type of hepatic encephalopathy: acute episodes of hepatic encephalopathy. • Type of liver disease: cirrhosis based on alcohol (80%), viral hepatitis (15%), or cryptogenic (5%). • Mean age: 57 years. • Proportion of men: 80%
Interventions	• Dopamine agent: levodopa (2 grams on the first day, then 4 grams/d) alone or with dopa-decarboxylase inhibitor (0.2 gram on the first day, then 0.4 grams/d). • Control: placebo. • Treatment duration: seven days.
Outcomes	• Hepatic encephalopathy and mortality.
Notes	• Health economics: not assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind placebo-controlled.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up described.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures defined and reported.
Sample size calculations	Unclear risk	Not reported.

Morgan 1980

Methods	• Cross-over trial.
Participants	• Type of hepatic encephalopathy: chronic hepatic encephalopathy. • Type of liver disease: cirrhosis due to alcohol (60%) or cryptogenic (40%). • Mean age: 51 years. • Proportion of men: 100%.
Interventions	• Dopamine agent: bromocriptine 15 mg/d. • Control: placebo. • Treatment duration: eight weeks.
Outcomes	• Hepatic encephalopathy, mortality, and adverse events.
Notes	• Health economics: not assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence.
Allocation concealment (selection bias)	Low risk	Central independent unit.
Blinding (performance bias and detection bias) All outcomes	Low risk	Administration of identical coded drug container.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures defined and reported.
Sample size calculations	Unclear risk	Not reported.

Uribe 1979

Methods	• Cross-over trial.
Participants	• Type of hepatic encephalopathy: chronic hepatic encephalopathy. • Type of liver disease: cirrhosis due to alcohol (63%) or viral hepatitis (37%). • Mean age: not reported (range 45 to 78 years). • Proportion of men: 63%.
Interventions	• Dopamine agent: bromocriptine 15 mg/d. • Control: placebo. • Treatment duration: two weeks.

Uribe 1979 *(Continued)*

Outcomes	• Hepatic encephalopathy, mortality, and adverse events.
Notes	• Health economics: not assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Central administration of blinded drug containers.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind placebo-controlled with additional blinded data analyses.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures defined and reported.
Sample size calculations	Unclear risk	Not reported.

Vij 1979

Methods	• Parallel-group trial.
Participants	• Type of hepatic encephalopathy: acute episode of hepatic encephalopathy. • Type of liver disease: fulminant liver failure due to viral hepatitis (100%). • Mean age: 32 years. • Proportion of men: not reported.
Interventions	• Dopamine agent: levodopa 3 to 4 grams/d. • Control: no intervention. • Treatment duration: not reported.
Outcomes	• Mortality.
Notes	• Health economics: not assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.

Vij 1979 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not described.
Selective reporting (reporting bias)	High risk	Hepatic encephalopathy not reported.
Sample size calculations	Unclear risk	Not reported.

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

Study	Reason for exclusion
Catalano 1982	Observational study.
Datta 1976	Observational study.
Jorge 1973	Observational study.
Lunzer 1974	Observational study.
Messner 1982	Randomised cross-over trial including 11 participants with chronic hepatic encephalopathy comparing bromocriptine with lactulose. Excluded because the control group received an active intervention.
Pascual 1979	Observational study.
Trovato 1982	Observational study.
Ubiria 1980	Observational study.
Uribe 1983	Randomised cross-over trial including four participants with chronic hepatic encephalopathy comparing bromocriptine versus neomycin. Excluded because the control group received an active intervention.

DATA AND ANALYSES

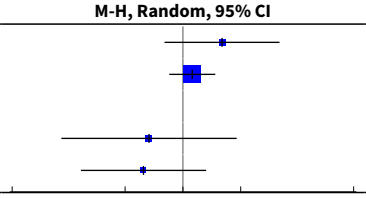
Comparison 1. Dopamine agonists versus placebo or no intervention

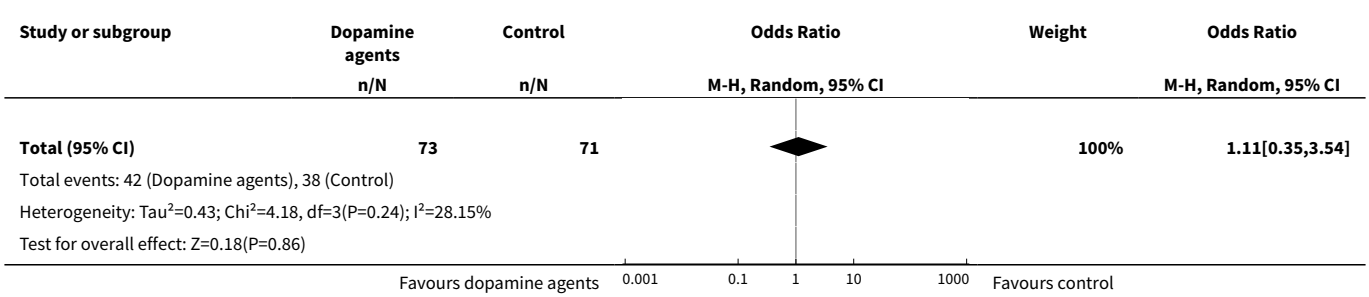
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5	144	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.35, 3.54]
2 Mortality stratified by type of hepatic encephalopathy	5	144	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.35, 3.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Acute episode of hepatic encephalopathy	3	131	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.34, 4.83]
2.2 Chronic hepatic encephalopathy	2	13	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.01, 8.52]
3 Mortality stratified by liver disease	5	144	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.35, 3.54]
3.1 Fulminant liver failure	2	56	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.05, 22.17]
3.2 Cirrhosis	3	88	Odds Ratio (M-H, Random, 95% CI)	1.30 [0.54, 3.15]
4 Mortality stratified by intervention	5	144	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.35, 3.54]
4.1 Levodopa	3	131	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.34, 4.83]
4.2 Bromocriptine	2	13	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.01, 8.52]
5 Mortality stratified by bias risk	5	144	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.59, 2.59]
5.1 Low bias risk	2	13	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.01, 8.52]
5.2 Unclear bias risk	3	131	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.63, 2.91]
6 Mortality stratified by trial design	5	144	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.35, 3.54]
6.1 Parallel group	3	131	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.34, 4.83]
6.2 Cross-over	2	13	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.01, 8.52]
7 Hepatic encephalopathy	2	80	Odds Ratio (M-H, Random, 95% CI)	2.99 [0.09, 100.55]
8 Hepatic encephalopathy paired data	3		Odds Ratio (Random, 95% CI)	0.68 [0.17, 2.67]
9 Adverse events paired data	2		OR (Random, 95% CI)	2.12 [-0.99, 5.24]

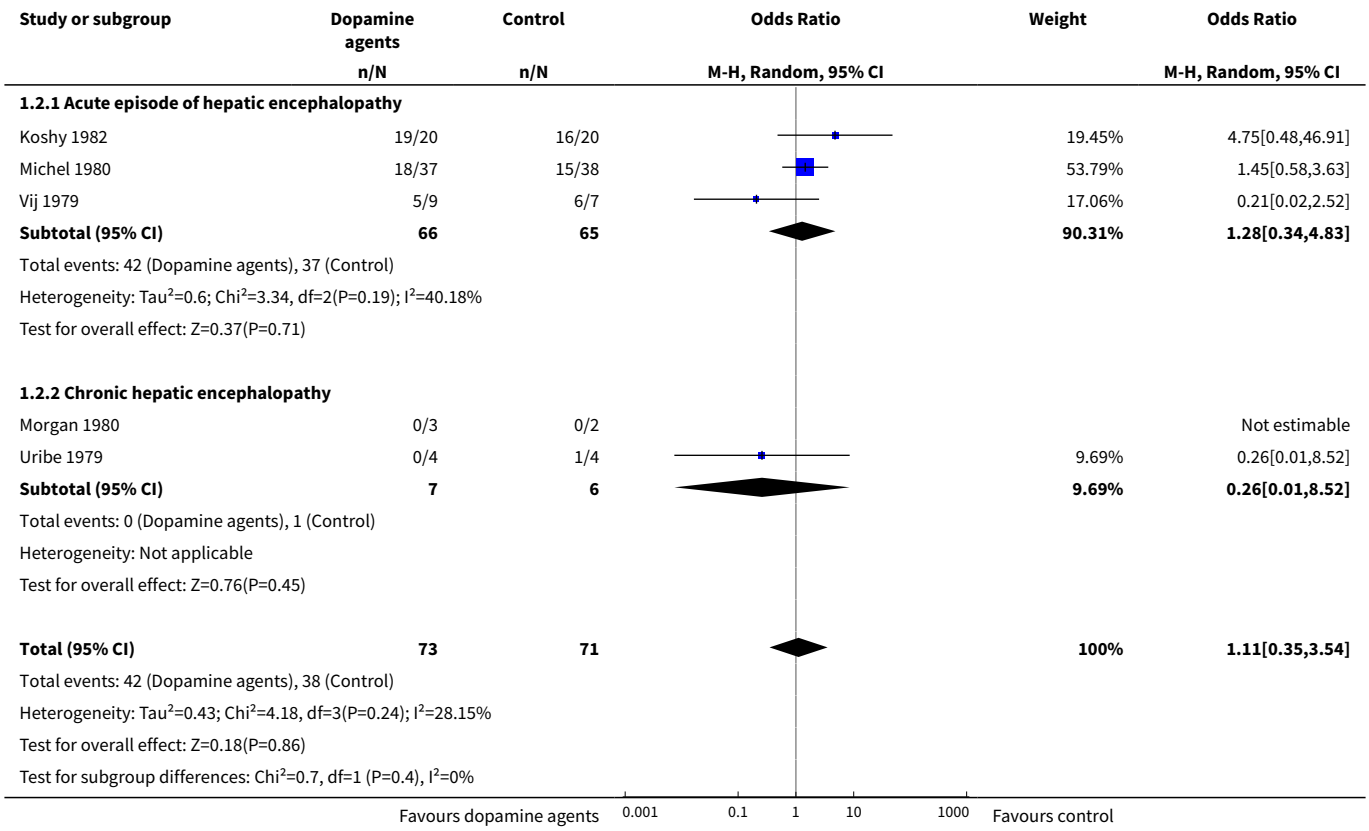
Analysis 1.1. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 1 Mortality.

Study or subgroup	Dopamine agents n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Koshy 1982	19/20	16/20		19.45%	4.75[0.48,46.91]
Michel 1980	18/37	15/38		53.79%	1.45[0.58,3.63]
Morgan 1980	0/3	0/2			Not estimable
Uribe 1979	0/4	1/4		9.69%	0.26[0.01,8.52]
Vij 1979	5/9	6/7		17.06%	0.21[0.02,2.52]

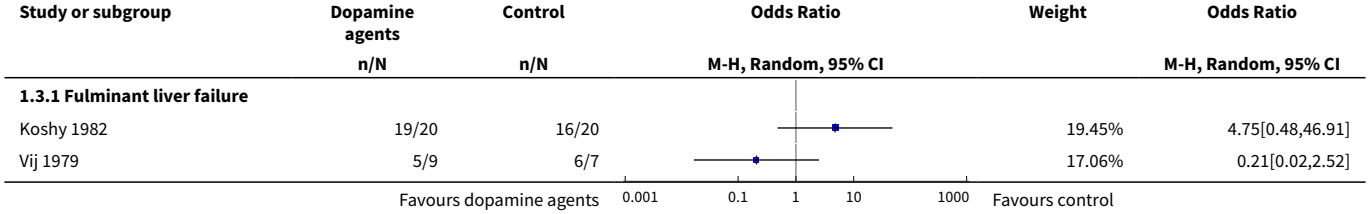


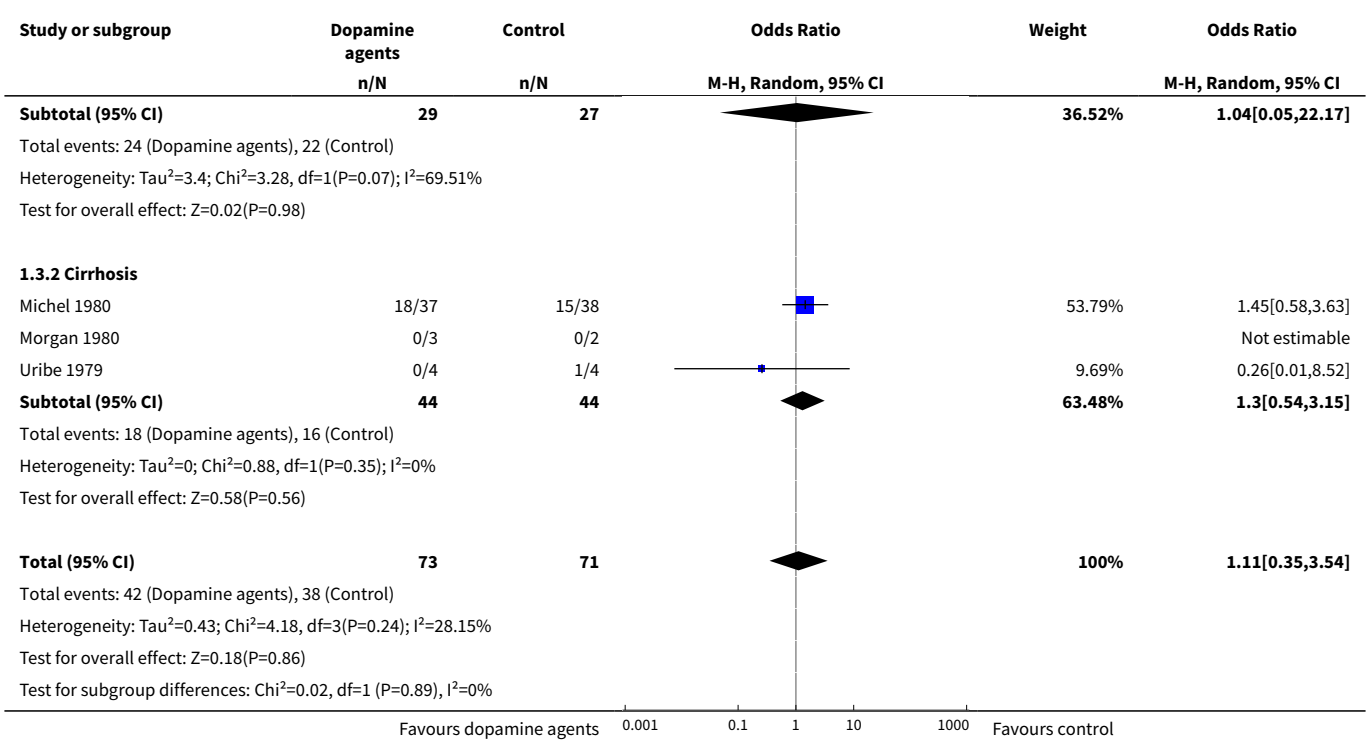


Analysis 1.2. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 2 Mortality stratified by type of hepatic encephalopathy.

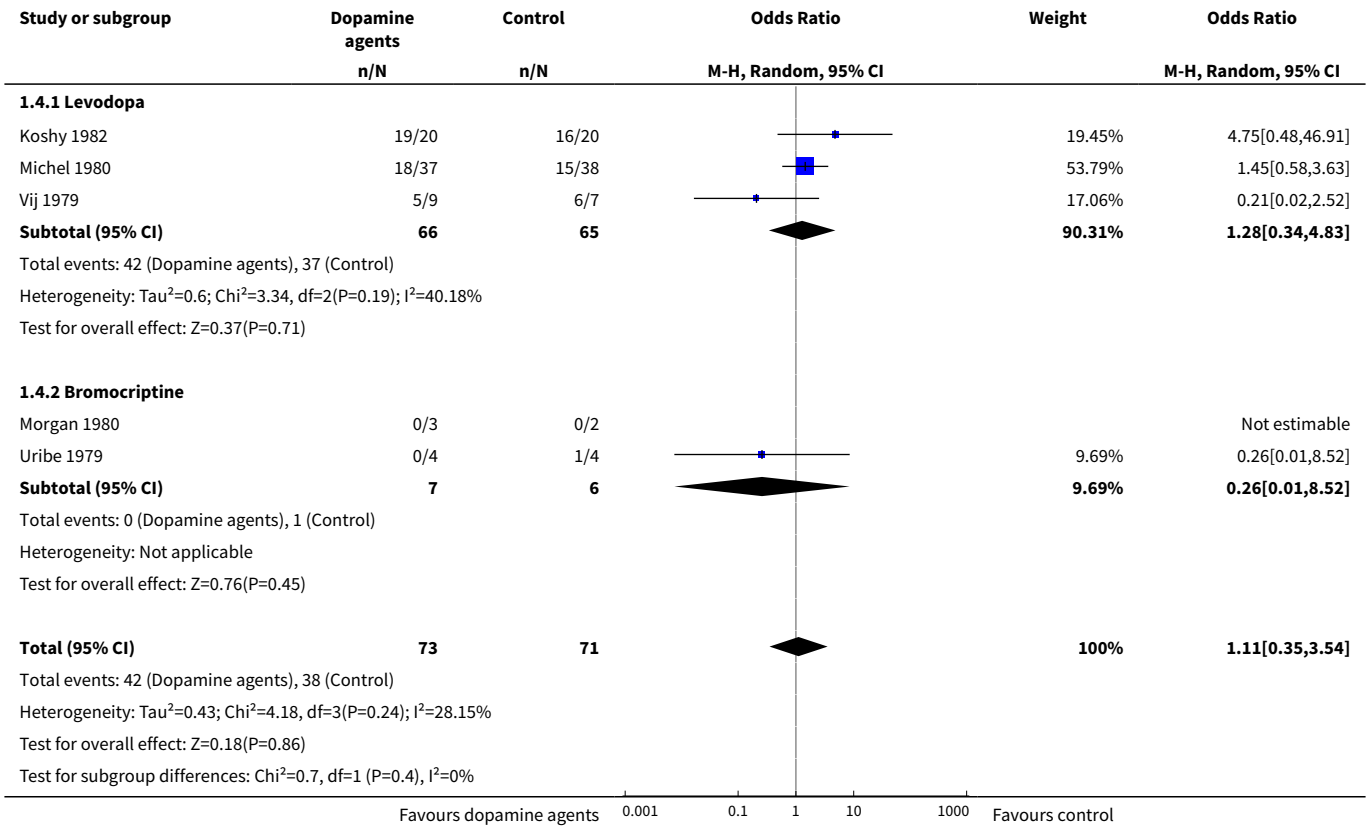


Analysis 1.3. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 3 Mortality stratified by liver disease.





Analysis 1.4. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 4 Mortality stratified by intervention.

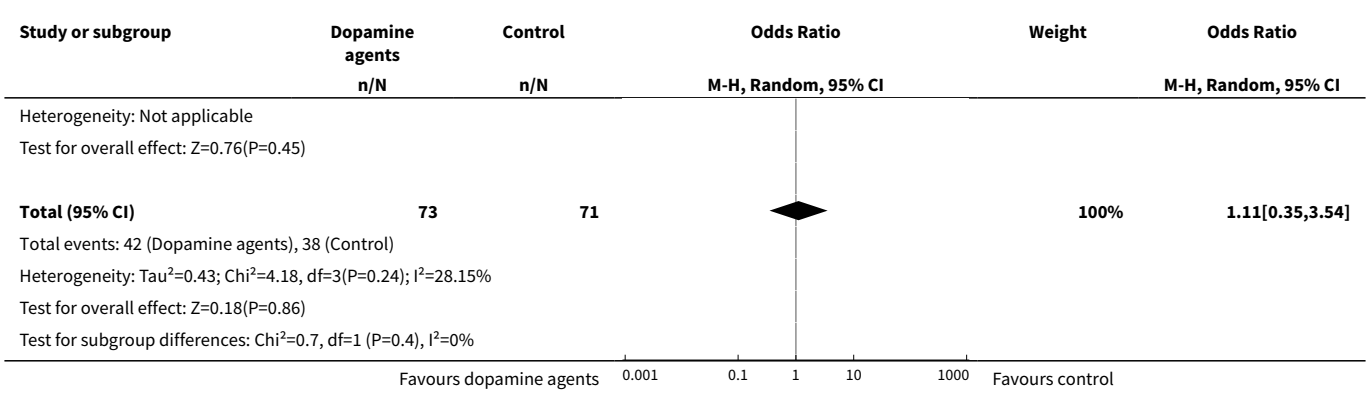


Analysis 1.5. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 5 Mortality stratified by bias risk.

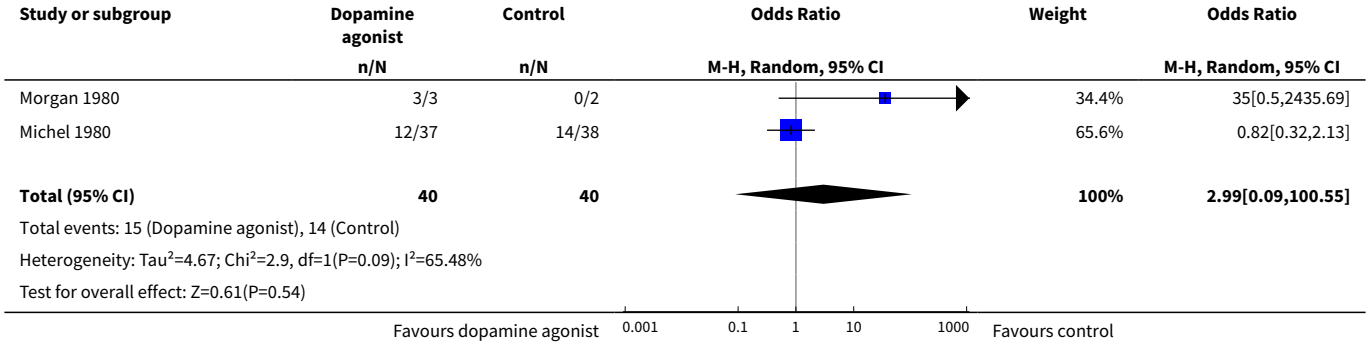
Study or subgroup	Dopamine agents n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Low bias risk					
Uribe 1979	0/4	1/4		10.59%	0.26[0.01,8.52]
Morgan 1980	0/3	0/2			Not estimable
Subtotal (95% CI)	**7**	**6**		**10.59%**	**0.26[0.01,8.52]**
Total events: 0 (Dopamine agents), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.76(P=0.45)					
1.5.2 Unclear bias risk					
Koshy 1982	19/20	16/20		6.27%	4.75[0.48,46.91]
Vij 1979	5/9	6/7		23.53%	0.21[0.02,2.52]
Michel 1980	18/37	15/38		59.61%	1.45[0.58,3.63]
Subtotal (95% CI)	**66**	**65**		**89.41%**	**1.36[0.63,2.91]**
Total events: 42 (Dopamine agents), 37 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.34, df=2(P=0.19); I^2=40.18%					
Test for overall effect: Z=0.78(P=0.43)					
Total (95% CI)	**73**	**71**		**100%**	**1.24[0.59,2.59]**
Total events: 42 (Dopamine agents), 38 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.18, df=3(P=0.24); I^2=28.15%					
Test for overall effect: Z=0.57(P=0.57)					
Test for subgroup differences: Chi^2=0.82, df=1 (P=0.36), I^2=0%					

Analysis 1.6. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 6 Mortality stratified by trial design.

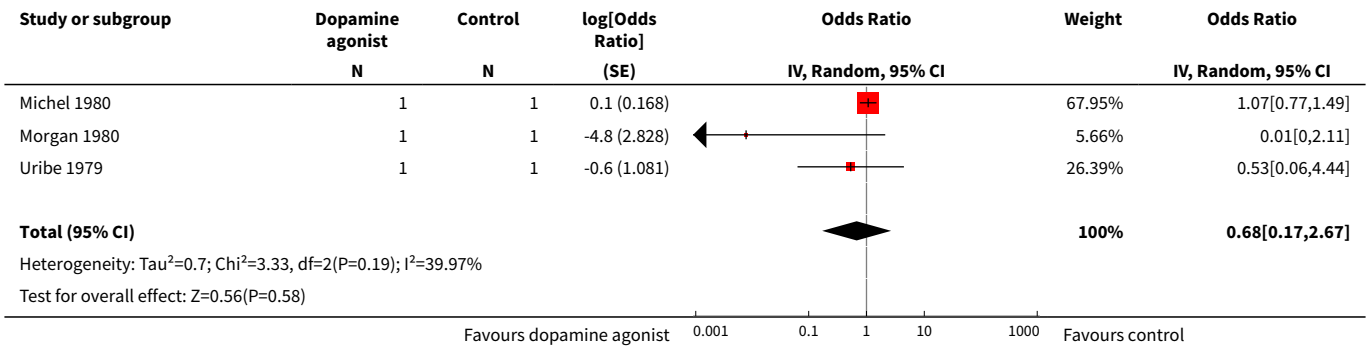
Study or subgroup	Dopamine agents n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.6.1 Parallel group					
Koshy 1982	19/20	16/20		19.45%	4.75[0.48,46.91]
Michel 1980	18/37	15/38		53.79%	1.45[0.58,3.63]
Vij 1979	5/9	6/7		17.06%	0.21[0.02,2.52]
Subtotal (95% CI)	**66**	**65**		**90.31%**	**1.28[0.34,4.83]**
Total events: 42 (Dopamine agents), 37 (Control)					
Heterogeneity: Tau^2=0.6; Chi^2=3.34, df=2(P=0.19); I^2=40.18%					
Test for overall effect: Z=0.37(P=0.71)					
1.6.2 Cross-over					
Morgan 1980	0/3	0/2			Not estimable
Uribe 1979	0/4	1/4		9.69%	0.26[0.01,8.52]
Subtotal (95% CI)	**7**	**6**		**9.69%**	**0.26[0.01,8.52]**
Total events: 0 (Dopamine agents), 1 (Control)					



Analysis 1.7. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 7 Hepatic encephalopathy.

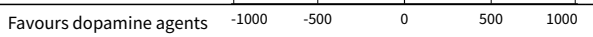


Analysis 1.8. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 8 Hepatic encephalopathy paired data.



Analysis 1.9. Comparison 1 Dopamine agonists versus placebo or no intervention, Outcome 9 Adverse events paired data.

Study or subgroup	Dopamine agonist N	Control N	OR (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Morgan 1980	1	1	1.3 (2.373)		44.87%	1.3[-3.35,5.95]
Uribe 1979	1	1	2.8 (2.14)		55.13%	2.79[-1.41,6.98]
Total (95% CI)					**100%**	**2.12[-0.99,5.24]**
Heterogeneity: Tau^2=0; Chi^2=0.22, df=1(P=0.64); I^2=0%						
Test for overall effect: Z=1.33(P=0.18)						



APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	January 2014.	(dopa* OR 'dopa decarboxylase' OR levodopa OR bromocriptine) AND ('liver cirrhosis' OR 'hepatic encephalopathy')
The Cochrane Central Register of Controlled Trials (CENTRAL)	Issue 12 of 12, 2013.	#1 MeSH descriptor: [Dopamine Agents] explode all trees #2 MeSH descriptor: [Dopa Decarboxylase] explode all trees #3 MeSH descriptor: [Levodopa] explode all trees #4 MeSH descriptor: [Bromocriptine] explode all trees #5 dopa* or dopa decarboxylase or levodopa or bromocriptine #6 #1 or #2 or #3 or #4 or #5 #7 MeSH descriptor: [Liver Cirrhosis] explode all trees #8 MeSH descriptor: [Hepatic Encephalopathy] explode all trees #9 (liver cirrhosis or hepatic encephalopathy) #10 #7 or #8 or #9 #11 #6 and #10
MEDLINE (Ovid SP)	1946 to January 2014.	1. exp Dopamine Agents/ 2. exp Dopa Decarboxylase/ 3. exp Levodopa/ 4. exp Bromocriptine/ 5. (dopa* or dopa decarboxylase or levodopa or bromocriptine).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, orig-

(Continued)

		inal title, abstract, name of substance word, subject heading word, unique identifier] 6. 1 or 2 or 3 or 4 or 5 7. exp Liver Cirrhosis/ 8. exp Hepatic Encephalopathy/ 9. (liver cirrhosis or hepatic encephalopathy).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 10. 7 or 8 or 9 11. 6 and 10 12. (random* or blind* or placebo* or meta-analysis).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 13. 11 and 12
EMBASE (Ovid SP)	1974 to January 2014.	1. exp dopamine receptor stimulating agent/ 2. exp dopamine receptor blocking agent/ 3. exp aromatic levo amino acid decarboxylase/ 4. exp LEVODOPA/ 5. exp BROMOCRIPTINE/ 6. (dopa* or dopa decarboxylase or levodopa or bromocriptine).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 7. 1 or 2 or 3 or 4 or 5 or 6 8. exp liver cirrhosis/ 9. exp hepatic encephalopathy/ 10. (liver cirrhosis or hepatic encephalopathy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 11. 8 or 9 or 10 12. 7 and 11 13. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 14. 12 and 13
Science Citation Index-Expanded (http://apps.webofknowledge.com)	1900 to January 2014.	#5 20 #4 AND #3 #4 1,186,796 TS=(random* or blind* or placebo* or meta-analysis) #3 205 #2 AND #1 #2 54,464 TS=(liver cirrhosis or hepatic encephalopathy)

(Continued)

#1 198,470 TS=(dopa* or dopa decarboxylase or levodopa or bromocriptine)

WHAT'S NEW

Date	Event	Description
13 January 2014	New citation required but conclusions have not changed	No new trials fulfilled the inclusion criteria of this review.
13 January 2014	New search has been performed	Searches were updated January 2014, but no new trials were identified for inclusion in the review. New trials are unlikely to be published in the following four years. The review has been updated based on current methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).
13 January 2012	Amended	AE Junker is the new, lead author of this first review update.

CONTRIBUTIONS OF AUTHORS

Anders Ellekær Junker (AEJ) and Lise Lotte Gluud (LLG) drafted the revised version of this updated review with methodology updates based on the most recent recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). AEJ, Bodil Als-Nielsen (BA-N), and LLG participated in the literature searches, identified trials eligible for inclusion, extracted data, and performed the statistical analyses. All authors revised the review and have approved the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Copenhagen Trial Unit, Denmark.

External sources

- The 1991 Pharmacy Foundation, Denmark.
- Danish Center for Evaluation and Health Technology Assessment (DACEHTA), Denmark.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We have changed the term 'dopaminergic agents' to the MeSH term 'dopamine agents' throughout the review.
- Based on reviewer comments, we have omitted the outcome 'Number of participants with hepatic encephalopathy recovery' because the definition of this outcome is highly variable. The outcome of (lack of) improvement in hepatic encephalopathy includes participants with complete as well as partial recovery from hepatic encephalopathy.
- In our original protocol, we planned to include health economics as an outcome. This outcome was omitted from our previous and present review on the basis of reviewer comments and evidence concerning the best methods for assessing this outcome. We have gathered data on whether health economics were assessed and have included these data in our table of included trials.
- Based on the most recent recommendations regarding the assessment of bias control, we have included bias tables and have assessed the bias control components of allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias (sample size assessments).
- We have included additional analyses on small-study effects (Egger's test).

INDEX TERMS

Medical Subject Headings (MeSH)

Bromocriptine [*therapeutic use]; Dopamine Agonists [*therapeutic use]; Hepatic Encephalopathy [*drug therapy]; Levodopa [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans