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Pentoxifylline for alcoholic hepatitis (Review)

Whitfield K, Rambaldi A, Wetterslev J, Gluud C

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Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007339.

DOI: 10.1002/14651858.CD007339.pub2.

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[Intervention Review]

Pentoxifylline for alcoholic hepatitis

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Editorial group: Cochrane Hepato-Biliary Group.

Publication status and date: New, published in Issue 1, 2010.

Citation: Whitfield K, Rambaldi A, Wetterslev J, Gluud C. Pentoxifylline for alcoholic hepatitis. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD007339. DOI: 10.1002/14651858.CD007339.pub2.

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ABSTRACT

Background

Alcoholic hepatitis is a life-threatening disease, with an average mortality of approximately 40%. There is no widely accepted, effective treatment for alcoholic hepatitis. Pentoxifylline is used to treat alcoholic hepatitis, but there has been no systematic review to assess its effects.

Objectives

To assess the benefits and harms of pentoxifylline in alcoholic hepatitis.

Search methods

The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, LILACS, clinicaltrials.gov, and full text searches were conducted until August 2009. Manufacturers and authors were contacted.

Selection criteria

All randomised clinical trials of pentoxifylline in participants with alcoholic hepatitis compared to control were selected for inclusion.

Data collection and analysis

Two authors extracted data and evaluated the risk of bias. RevMan Analysis was used for statistical analysis of dichotomous data with risk ratio (RR) and of continuous data with mean difference (MD), both with 95% confidence intervals (CI). Trial sequential analysis (TSA) was also used for statistical analysis of dichotomous and continuous data in order to control for random error. Where data were only available from one trial, we used Fisher's exact test or Student's t-test.

Main results

Five trials, with a total of 336 randomised participants, were included. A total of 105 participants (31%) died. Of the five included trials, four (80%) had a high risk of bias. Meta-analysis using all five trials showed that pentoxifylline reduced mortality compared with control (RR 0.64; 95% CI 0.46 to 0.89). However, this result was not supported by trial sequential analysis, which adjusts for multiple testing on accumulating data. Furthermore, four of the five trials were judged to have a high risk of bias, thus risking an overestimated intervention effect. Meta-analysis showed that pentoxifylline reduced the hepatic-related mortality due to hepatorenal syndrome (RR 0.40; 95% CI 0.22 to 0.71), but trial sequential analysis did not support this result. Data from one trial suggests that pentoxifylline may increase the occurrence of serious and non-serious adverse events compared to control.

Pentoxifylline for alcoholic hepatitis (Review)

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Authors' conclusions

The current available data may indicate a possible positive intervention effect of pentoxifylline on all-cause mortality and mortality due to hepatorenal syndrome, and conversely, an increase in serious and non-serious adverse events. However, the evidence is not firm; no conclusions can be drawn regarding whether pentoxifylline has a positive, negative, or neutral effect on participants with alcoholic hepatitis.

PLAIN LANGUAGE SUMMARY

Not enough evidence to conclude the effect of pentoxifylline on patients with alcoholic hepatitis

Hepatitis is inflammatory injury of the liver. Alcohol is toxic to the liver, and too much alcohol can cause alcoholic hepatitis. The severe form of alcoholic hepatitis is life-threatening. The use of pentoxifylline as a treatment for alcoholic hepatitis cannot be supported or rejected based on the best evidence available today. We found five randomised trials, which together included 336 participants; half received pentoxifylline, and the other half received placebo or no intervention. We performed this systematic review and statistical analyses but could not show firm evidence of beneficial effects of pentoxifylline on mortality or on complications of liver diseases in patients with alcoholic hepatitis. Pentoxifylline did appear to cause more serious and non-serious side effects. In order to help decide whether pentoxifylline should be used to treat alcoholic hepatitis or not, we need well-designed, well-conducted, large randomised clinical trials, with short-term (less than one month) and long-term (more than one month) data on benefits and harms.

BACKGROUND

Excessive and chronic ingestion of alcohol can lead to alcoholic hepatitis. Hepatitis is injury to the liver and can be caused by the toxins in alcohol. Severe alcoholic hepatitis has a wide range of clinical symptoms including fever, liver enlargement, gastrointestinal bleeding, and jaundice (Madhotra 2003; Ceccanti 2006). It is frequently quoted that mortality in patients with severe alcoholic hepatitis is up to 60% (Hardison 1966). However, reliable and up-to-date information regarding alcoholic hepatitis-associated mortality is not readily available. Data from a Cochrane review on randomised clinical trials with glucocorticosteroids for alcoholic hepatitis in the last 35 years show that mortality in the non-intervention or placebo group of participants was approximately 40% (Rambaldi 2009).

Therapeutic agents used for alcoholic hepatitis include glucocorticosteroids and, as a more experimental treatment, tumour necrosis factor inhibitors (Madhotra 2003; Rongey 2006). Currently, glucocorticosteroids are the most common treatment for severe alcoholic hepatitis and are recommended by the American College of Gastroenterology (McCullough 1998). The effectiveness of glucocorticosteroids as a treatment for alcoholic hepatitis is, however, controversial because meta-analyses of randomised clinical trials have yielded conflicting results (Imperiale 1990; Poynard 1991; Christensen 1995; Gluud 2001; Rambaldi 2009).

Pentoxifylline is a xanthine derivative; one of its effects is to act

as a weak inhibitor of the cytokine, tumour necrosis factor. Tumour necrosis factor and other cytokines play an important role in the pathophysiology of alcoholic liver disease (McClain 1989; Levitsky 2004). Some randomised clinical trials have reported that pentoxifylline reduces renal impairment in participants with severe alcoholic hepatitis (McHutchison 1991; Akriviadis 2000; Sidhu 2006). Of these trials two reported improved short-term survival in participants with severe alcoholic hepatitis (McHutchison 1991; Akriviadis 2000). In contrast, however, a randomised clinical trial of pentoxifylline for advanced liver cirrhosis reported on a subgroup analysis of participants with severe acute alcoholic hepatitis and showed that pentoxifylline had no significant effect on mortality (Lebrec 2007).

We could not identify systematic reviews or meta-analyses on pentoxifylline for alcoholic hepatitis. We have, therefore, undertaken this Cochrane Hepato-Biliary Group systematic review.

OBJECTIVES

To assess the benefits and harms of pentoxifylline versus placebo or no intervention in participants with alcoholic hepatitis.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion randomised clinical trials irrespective of blinding, language, publication year, or publication status. For assessment of harm we also considered quasi-randomised studies and observational studies.

Types of participants

We included participants with alcoholic hepatitis, ie, patients with alcoholic hepatitis who satisfied the inclusion criteria of each trial.

Types of interventions

We included trials, which administered pentoxifylline at any dose or duration versus placebo or no intervention. We included one trial, which used standard therapy as a co-intervention in both groups (Lebrec 2007).

Types of outcome measures

Primary outcome measures

1. All-cause mortality and hepatic-related mortality.

Secondary outcome measures

1. Hepatic-related morbidity (eg, ascites, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome etc).
2. Liver and kidney biochemistry and function (eg, serum (s)-bilirubin, prothrombin time (PT), s-albumin, s-aspartate aminotransferase (AST), s-alanine aminotransferase (ALT), s-alkaline phosphatases (AP), s-gamma-glutamyl transferase (GGT).
3. Liver histology.
4. Adverse events (as defined by the trialists or by the International Conference on Harmonisation guideline for Good Clinical Practice (ICH-GCP 1996)).
5. Quality of life.
6. Post-hoc outcome measures, TNF levels (this was not a pre-planned analysis).

Search methods for identification of studies

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2009), the *Cochrane Central Register of Controlled Trials* (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, *Science Citation Index Expanded*, LILACS, and *Clinical Trials.gov* (Royle 2003). The search strategies and the time span of

the searches are given in [Appendix 1](#). We used the reference lists of the identified studies to identify further clinical trials. We contacted the authors of the identified trials and the pharmaceutical companies involved in the production of pentoxifylline products to request details regarding additional clinical trials.

Data collection and analysis

We conducted the review according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) and the *Cochrane Hepato-Biliary Group Module* (Gluud 2009).

Trial identification

Two authors (KW and AR) independently identified trials for inclusion. In the first round of selection, titles and abstracts were assessed and irrelevant articles were excluded. In the second round of selection, full-text articles were assessed and those which satisfied the inclusion criteria were selected. We have listed the excluded trials with the reasons for their exclusion ([Characteristics of excluded studies](#)).

Data extraction

We independently extracted data from the trials (KW and AR), and differences in opinion were resolved by discussion with CG. The following data were extracted:

Publication

1. Year of publication.
2. Year of trial.
3. First author.
4. Language.
5. Country.
6. Number of participants.

Trial design

1. Inclusion/exclusion criteria.
2. Dose of pentoxifylline (route of administration, frequency, duration).
3. Placebo or no intervention.
4. Co-interventions.
5. Outcome measures (as described above).
6. Period of follow-up.
7. Methodological quality (as described below).
8. Sample size calculation.
9. Intention-to-treat analysis.

Participant characteristics, diagnosis, and interventions

1. Characteristics of trial participants and of those excluded from the trial (mean or median age, sex ratio, duration of alcoholic hepatitis, severity of alcoholic hepatitis (alcoholic hepatitis was considered severe if the patient has a Maddrey's score of at least 32 and/or presence of spontaneous hepatic encephalopathy (Maddrey 1978), alcohol consumption, other baseline characteristics as described by the trialists).
2. Development of clinical features and complications.
3. Liver and kidney biochemistry and function (as described above).
4. Liver histology.
5. Adverse events (as described above).
6. Quality of life.

We contacted the trial authors in order to clarify or obtain any information that was lacking or not clearly described in the published trial. We considered potential confounding variables by examining the participants' baseline characteristics.

Assessment of risk of bias

Due to the risk of overestimation of the intervention effects in randomised trials with a high risk of bias (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008), we independently assessed the risk of bias of the trials, without masking the trial names (KW and AR). We followed the instructions detailed in the *Cochrane Handbook for Systematic Reviews and Interventions* (Higgins 2008) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2009). We assessed the risk of bias of the randomised clinical trials using five components: sequence generation; allocation concealment; blinding; handling of incomplete outcome data, ie, follow-up; and selective outcome reporting. We also extracted data relating to any other bias, eg, early stopping, baseline imbalance, source of funding. The risk of bias components were assessed according to the definitions below.

If relevant information was not available in the published trial, we contacted the authors in order to assess the trials correctly.

Sequence generation

- Adequate, sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.
- Unclear, the trial is described as randomised but the method of sequence generation was not specified.
- Inadequate, the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and was excluded for the assessment of benefits but not for harms.

Allocation concealment

- Adequate, allocation was controlled by a central and independent randomisation unit, opaque and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
- Unclear, the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies was excluded for the assessment of benefits but not for harms.

Blinding

- Adequate, the trial was described as double blind and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
- Unclear, the trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
- Not performed, the trial was not double blind, so that the allocation was known during the trial.

Incomplete outcome data

- Adequate, 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, the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

- Adequate, pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
- Unclear, not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, it is unclear whether data on these outcomes were recorded or not.
- Inadequate, one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Other biases

Early stopping

- Adequate, if sample size calculation was reported and the trial was not stopped or the trial was not stopped early by formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was low.
- Unclear, if sample size calculation was not reported and it is not clear whether the trial was stopped early or not.
- Inadequate, if the trial was stopped early due to an informal stopping rule or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high.

Baseline imbalance

- Adequate, if there was no baseline imbalance in important characteristics.
- Unclear, if the baseline characteristics were not reported.
- Inadequate, if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Source of funding

- No risk of for-profit bias, if the trial's source of funding did not come from parties that might have a conflicting interest (eg, a pentoxifylline manufacturer).
- Unclear, if the source of funding was not clear.
- Risk of for-profit bias, if the trial was funded by a drug manufacturer.

Trials with adequate sequence generation, adequate allocation concealment, adequate blinding, adequate handling of incomplete outcome data, and adequate selective outcome reporting were considered low-bias risk trials. Trials with one or more unclear or inadequate quality component were considered high-bias risk trials (Gluud 2009).

Intention-to-treat analysis

We analysed data according to the intention-to-treat principle, whereby all of the participants entered (or randomised) in each trial were included in the analysis. Participants who were lost to follow-up were, initially, considered survivors. Furthermore, sensitivity analyses were subsequently performed whereby those participants lost to follow-up were analysed according to different possible outcome scenarios. The sensitivity analyses are described below.

Statistical methods

We used the statistical software RevMan 5 provided by The Cochrane Collaboration (RevMan 2008). We calculated risk ratio (RR) with 95% confidence interval (CI) for dichotomous variables, and we used mean differences (MD) with 95% CI for continuous variables, using both the random-effects model (DerSimonian 1986) and the fixed-effect model (DeMets 1987) with the significant level less than or equal to P 0.05. When there were discrepancies in the statistical significance of the results between the two models, we reported the results of both models; otherwise we reported the results from only the fixed-effect model. We explored the presence of statistical heterogeneity by the chi-squared test with significance less than or equal to P 0.1 and measured the quantity of heterogeneity by I^2 (Higgins 2002). Where data were only available from one trial, we used Fisher's exact test (Fisher 1922) for dichotomous data and Student's t-test (Student 1908) for continuous data.

Trial sequential analysis

In order to control for risk of random error, we performed trial sequential analysis (TSA) for the dichotomous outcomes all-cause mortality, hepatic-related morbidity, hepatorenal syndrome as well as for the continuous outcomes tumour necrosis factor, serum bilirubin and serum creatinine (Brok 2008; Brok 2008a; Thorlund 2008; Wetterslev 2008).

Subgroup analyses

We performed subgroup analyses on trials with low risk of bias compared to trials with high risk of bias (as described above). Comparison of intervention effects was conducted with test of interaction (Altman 2003). We intended to perform subgroup analyses on participants with severe alcoholic hepatitis compared to participants with mild alcoholic hepatitis; however, this was not possible as all participants had the severe form of the disease.

Sensitivity analyses

We assessed the effect of missing outcome data on the primary outcome measure all-cause mortality by applying a number of different scenarios to the intention-to-treat analyses. These scenarios are described in *The Cochrane Hepato-Biliary Group Module* (Gluud 2009) and are defined as the following:

1. Poor outcome analysis: assumes that all of the participants with missing data (from either group) died.
2. Good outcome analysis: assumes that none of the participants with missing data (from either group) died.
3. Extreme-case favouring pentoxifylline: assumes that none of the participants with missing data from the pentoxifylline group died, whereas all of those from the control group died.

4. Extreme-case favouring control: assumes that all of the participants with missing data from the pentoxifylline group died, whereas none from the control group died.

Bias exploration

We intended to use funnel plot graphs in order to inform us of the likelihood of bias in the meta-analysis. Asymmetry in a funnel plot can indicate, for example, high risk of a number of types of bias, including publication bias (Begg 1994; Egger 1997). However, asymmetry in a funnel plot alone is not a precise indicator for the presence of bias (Rücker 2008). A recently proposed arcsine test is a more precise indicator of the presence or absence of bias (Rücker 2008). If asymmetry in the funnel plot had occurred, then we planned to undertake the arcsine test to determine if bias is present or not. We did not perform a funnel plot or a subsequent arcsine test as we did not have the recommended minimal number of ten or more trials in any meta-analyses.

RESULTS

Description of studies

Our search strategy identified 149 publications, out of which 35 were duplicates. Of the remaining 114 publications, 100 were excluded in the first round of assessment, either because they were reviews or because they did not relate to alcoholic hepatitis. A further seven publications were excluded in the second round of assessment because they did not describe randomised clinical trials investigating the effect of pentoxifylline on participants with alcoholic hepatitis (Characteristics of excluded studies).

We identified a total of seven publications referring to five randomised clinical trials in our systematic review (Characteristics of included studies). One of the trials was published as an abstract and as a full text (Akriviadis 2000). The remaining four trials were all published as abstracts only (McHutchison 1991; Paladugu 2006; Sidhu 2006; Lebrek 2007). The primary authors were contacted

for further information and data relating to the trials. Didier Lebrek responded and kindly provided data on the number of participants in each intervention group and on outcome measures (Lebrek 2007). No other responses have so far been received.

We contacted manufacturers of pentoxifylline and pentoxifylline products and asked for any information about unpublished or on-going trials using pentoxifylline involving participants with alcoholic hepatitis. ALS Scandinavia AB and Mylan Inc. replied, and stated that they did not know of any further publications nor ongoing trials. Sanofi-Aventis replied informing us of the Lebrek trial (Lebrek 2007), which we had already identified in our search strategy.

In addition, through a search for ongoing trials in clinicaltrials.gov registry we identified two ongoing trials. These trials have been classified as ongoing studies (NCT00205049; NCT00388323). The trial NCT00205049a has been completed, but there is no publication to date.

Included studies

We identified and included five randomised clinical trials, which assessed the effect of pentoxifylline in a total of 336 participants with alcoholic hepatitis. Four of the five included trials were reported as abstracts only. Four of the five included trials were judged to be at high risk of bias. The trials took place in the USA, France, and India. From the publications which reported sex and age of the participants, more than 90% were male, and the average age was 44 years old. In each trial, all participants had the severe form of alcoholic hepatitis and all trials reported on mortality.

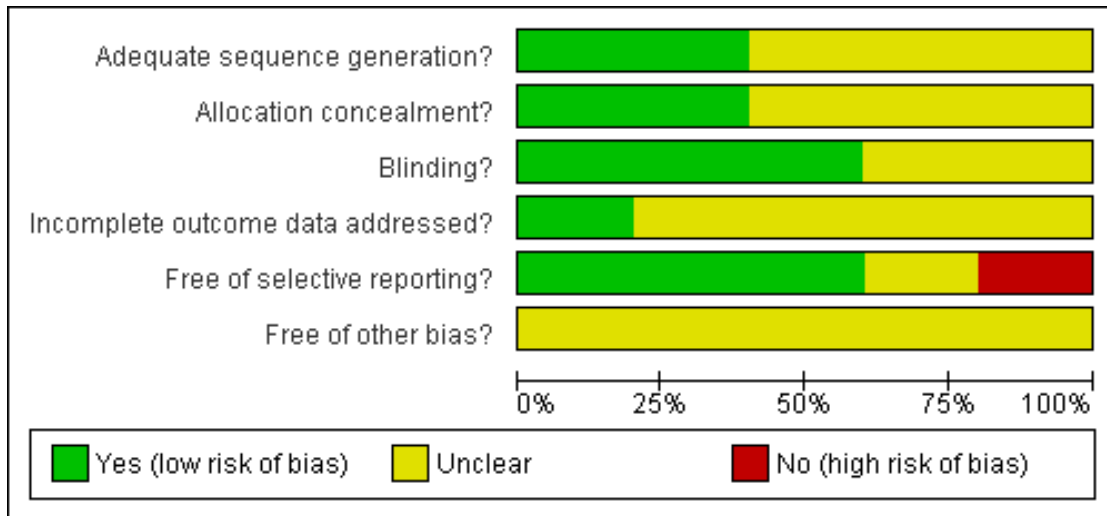
Risk of bias in included studies

Risk of bias was assessed according to five components: sequence generation; allocation concealment; blinding; handling of incomplete outcome data; and selective outcome reporting. Of the five included trials, one was assessed as having a low risk of bias (Akriviadis 2000) and four were assessed as having a high risk of bias (McHutchison 1991; Paladugu 2006; Sidhu 2006; Lebrek 2007) (Figure 1). Statistical analyses which include all five trials are therefore based primarily on high risk of bias trials (Figure 2).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Akriviadis 2000	+	+	+	+	+	?
Lebrec 2007	+	+	+	?	?	?
McHutchison 1991	?	?	?	?	-	?
Paladugu 2006	?	?	?	?	+	?
Sidhu 2006	?	?	+	?	+	?

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



Effects of interventions

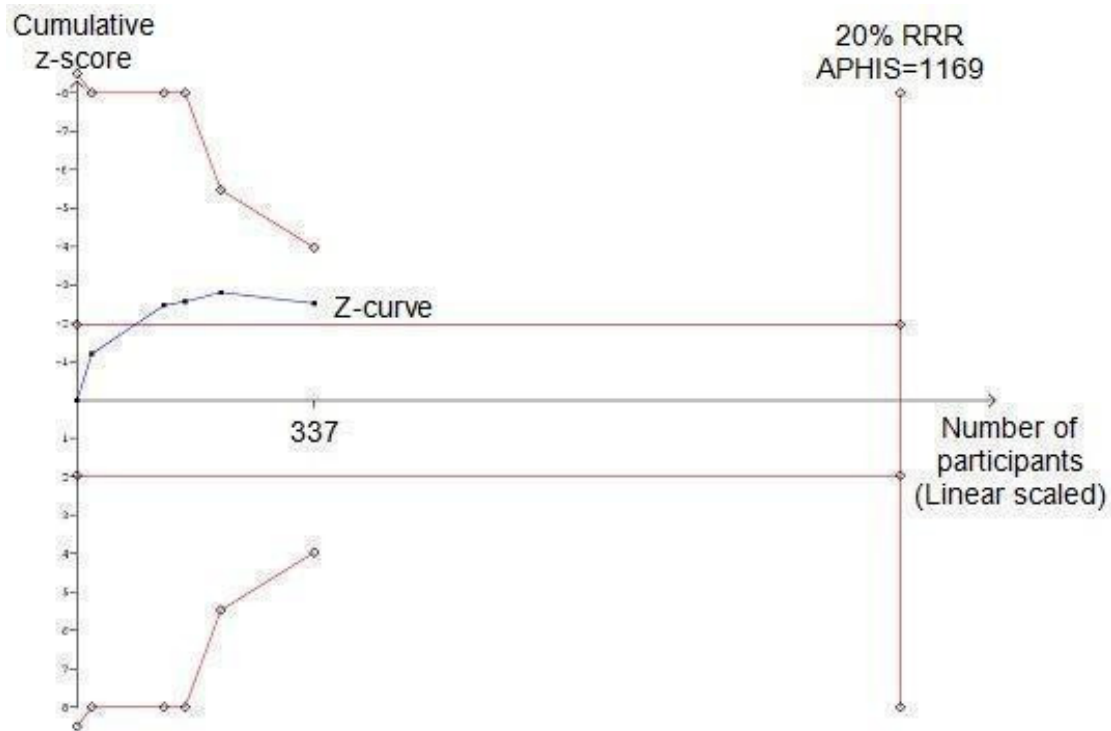
All-cause mortality

Meta-analysis on data for all-cause mortality shows that pentoxifylline significantly reduced mortality in participants with alcoholic hepatitis compared to control (RR 0.64; 95% CI 0.46 to 0.89, fixed-effect model) (Analysis 1.1). The heterogeneity was measured as having I² equal to 0% (Analysis 1.1). The result from the fixed-effect model concurred with that from the random-effects model (Analysis 1.2).

In contrast, trial sequential analysis on data for all-cause mortality

does not support a 20% risk ratio reduction of all-cause mortality in the pentoxifylline group compared to control (Figure 3). Trial sequential analysis is a statistical method, which controls for random error caused by formal or informal repetitive testing of accumulating data, so this can be considered a more robust result. The result of the trial sequential analysis is shown by the cumulated z-curve (blue curve), which does not cross the trial sequential monitoring boundary (red curve), thus implying that there is no firm evidence for an intervention effect of 20% risk ratio reduction (RRR) (Figure 3).

Figure 3. Trial sequential analysis of the cumulative meta-analysis of the effect of pentoxifylline on all-cause mortality in participants with alcoholic hepatitis. The required information size of 1169 is calculated based on an a priori intervention effect of 20% (APHIS), a risk of type I error of 5%, and a power of 80%. The event rate in the control group is 39%, which is based on a meta-analytic estimate of the control event rate of all the included trials. Although the cumulated z-curve (blue curve) crosses the traditional boundary of 5% significance (horizontal red line), it does not cross the trial sequential monitoring boundary (red curve), implying that there is no firm evidence for an effect of 20% risk ratio reduction (RRR) when the cumulative meta-analysis is adjusted for multiple testing on accumulating data.



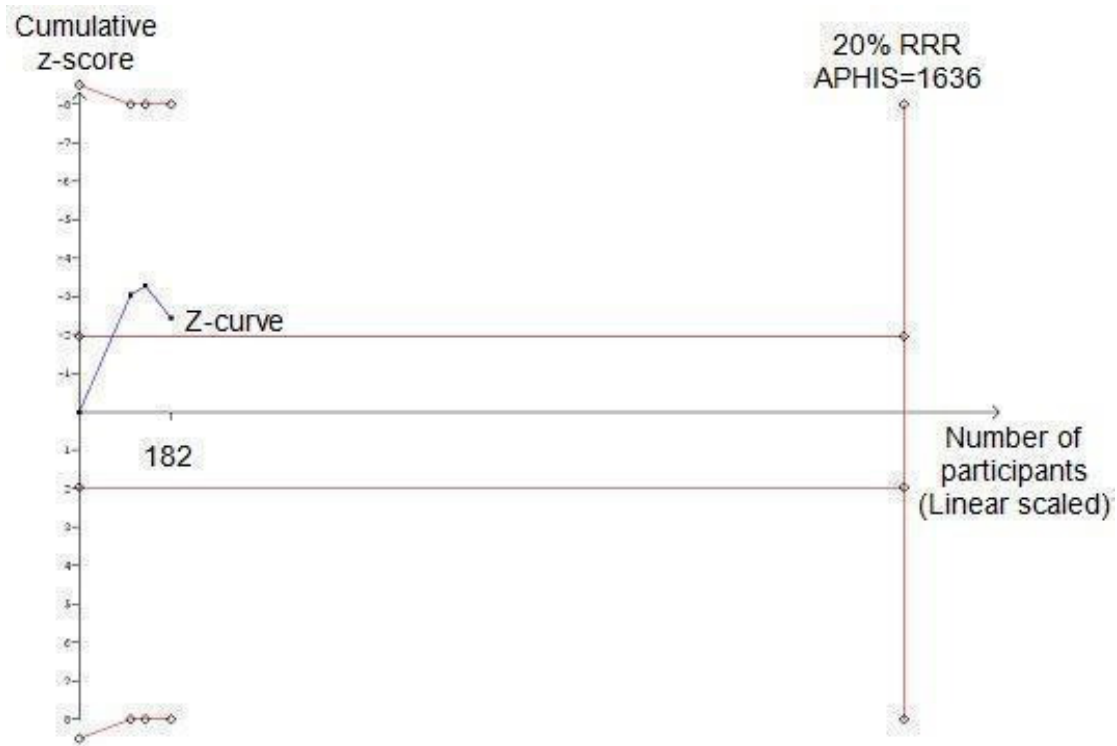
Hepatic-related mortality

Three trials reported data on hepatic-related mortality (Akriviadis 2000; Paladugu 2006; Sidhu 2006). In all cases, hepatic-related mortality was caused by hepatorenal syndrome. Hepatic-related mortality occurred in 13/89 (15%) and 34/93 (37%) participants in the pentoxifylline and control groups, respectively (RR 0.40; 95% CI 0.22 to 0.71) (Analysis 2.1). Reduction in hepatic-related mortality in the pentoxifylline group is statistically significant (Analysis 2.1). The statistical heterogeneity of this meta-analysis has an I^2 of 22%; there was no discrepancy between the fixed-effect and random-effects models, so we only report the fixed-

effect model.

In contrast, heterogeneity-adjusted trial sequential analysis of these data does not support a 20% risk ratio reduction of hepatic-related mortality in the pentoxifylline group compared to the control group (Figure 4). We consider that the result from the trial sequential analysis is more robust than that from a meta-analysis because it controls for random error caused by formal or informal repetitive testing on accumulating data. The result is shown by the cumulated z-curve (blue curve); the z-curve does not cross the trial sequential monitoring boundary (red curve), thus implying that there is no firm evidence for an intervention effect of 20% risk ratio reduction (RRR) (Figure 4).

Figure 4. Trial sequential analysis of the cumulative meta-analysis of the effect of pentoxifylline on hepatic-related mortality in participants with alcoholic hepatitis. The required information size of 1636 is calculated based on an a priori intervention effect of 20% (APHIS), a risk of type I error of 5% and a power of 80%. The event rate in the control group is 38%, which is based on a meta-analytic estimate of the control event rate of all the included trials. Although the cumulated z-curve (blue curve) crosses the traditional boundary of 5% significance (horizontal red line), it does not cross the trial sequential monitoring boundary (red curve), implying that there is no firm evidence for an effect of 20% risk ratio reduction (RRR) when the cumulative meta-analysis is adjusted for multiple testing on accumulating data.



Subgroup analysis of all-cause mortality according to risk of bias

Subgroup analysis was performed in order to compare trials with low risk of bias to those with high risk of bias. One trial was assessed as having a low risk of bias (Akriviadis 2000) and four trials were assessed as having a high risk of bias (McHutchison 1991; Paladugu 2006; Sidhu 2006; Lebec 2007) (Figure 1). The trial with low risk of bias reports that pentoxifylline decreased mortality; this result is statistically significant (RR 0.52; 95% CI 0.29 to 0.92) (Analysis 1.3). In a meta-analysis using the four trials with high risk of bias, pentoxifylline decreased mortality but to a lesser extent (RR 0.71; 95% CI 0.48 to 1.07). This result was not statistically significant.

To assess whether the risk ratios from the meta-analyses of the different subgroups were significantly different from each other,

a test of interaction was performed (Altman 2003). The test of interaction gave a z statistic of 0.9 with corresponding P value 0.37, showing that the difference between the intervention effects is not statistically significant.

Subgroup analysis of all-cause mortality according to severe or not severe alcoholic hepatitis

Alcoholic hepatitis was considered severe in all of the trials and in all of the included participants. As such, a subgroup analysis comparing all-cause mortality according to severe and non-severe forms of alcoholic hepatitis was not possible.

Sensitivity analysis according to different possible outcomes experienced by those trial participants

with missing data

Only one trial reported the withdrawals and drop-outs of participants (Akriviadis 2000). In total there were 16 randomised participants who did not contribute a complete set of outcome data. The reasons for withdrawal were reported and mortality data were collected for 15, with all having survived. Therefore, there was only one participant in all five of the included trials whose outcome data on all-cause mortality is missing. In the sensitivity analysis this single participant was considered to have survived or to have died (Analysis 3.1). In both cases pentoxifylline reduced all-cause mortality, and the results were statistically significant in both scenarios (presumed to have survived: RR 0.64; 95% CI 0.46 to 0.89 and presumed to have died: RR 0.66; 95% CI 0.48 to 0.91). This sensitivity analysis showed that the results of the meta-analysis are not affected by the missing outcome data.

Secondary outcome measures

Hepatic-related morbidity

Three trials reported on hepatic-related morbidity (Akriviadis 2000; Paladugu 2006; Sidhu 2006). Variceal haemorrhage occurred in 4/64 (6%) and 2/68 (3%) participants in the pentoxifylline and control groups, respectively (RR 2.18; 95% CI 0.42 to 11.3) (Analysis 4.1). Hepatic encephalopathy occurred in 9/50 (18%) and 13/52 (25%) participants in the pentoxifylline and control groups, respectively. Statistical significance was determined using Fisher's exact test ($P = 0.133$) (Table 1). Neither result for variceal haemorrhage nor hepatic encephalopathy was statistically significant.

These three trials also reported on hepatorenal syndrome, all occurrences of which resulted in hepatic-related mortality, and the results are described above.

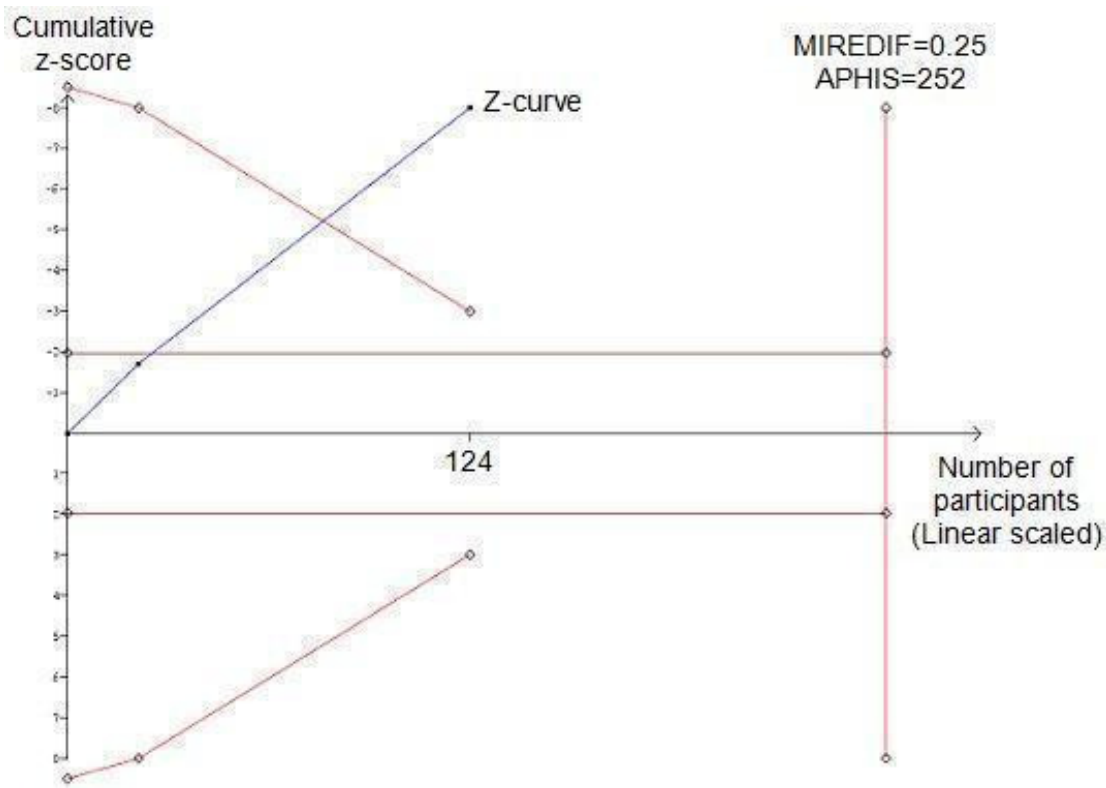
Liver and kidney biochemistry and function

Only two trials reported data on liver and kidney biochemistry and function (McHutchison 1991; Akriviadis 2000). Some standard errors were reported as standard error of the mean; therefore, we converted them to standard deviation (Analysis 5.1; Analysis 5.2, Table 2). The results reported in Akriviadis 2000 are depicted graphically in the published article, and we extracted data from the graphs. The data are reported as means, with either standard error of the mean or standard deviations; however, this information has not been described in the figure legend. We have judged whether standard error of the mean or standard deviation is reported based on the magnitude of the error bars and on the standard deviations for laboratory values at randomisation given in a data table in the trial report (Akriviadis 2000).

Analysis of the data from Akriviadis 2000 shows blood urea nitrogen (mg/dl) is lower in the pentoxifylline group than the control group; statistical significance was determined using the Student's t-test; the result was statistically significant ($P = 0.021$) (Table 2). Analysis of the data on prothrombin time (seconds) from Akriviadis 2000 shows that there is no difference in prothrombin time in the two groups (Table 2). Statistical significance was determined using the Student's t-test; the result was not statistically significant ($P = 1$) (Table 2).

Meta-analysis shows a decrease in serum creatinine (mg/dl) in the pentoxifylline group; this is statistically significant (MD -1.00; 95% CI -1.14 to -0.87) (Analysis 5.1). Trial sequential analysis of these data supports the finding in the meta-analysis. The z-curve (blue curve) crosses the trial sequential monitoring boundary implying that there is firm evidence for a decrease of 0.25 (mg/dl) serum creatinine in the pentoxifylline group (Figure 5).

Figure 5. Trial sequential analysis of the cumulative meta-analysis of the effect of pentoxifylline on serum creatinine in participants with alcoholic hepatitis. The required information size of 252 is calculated based on an intervention effect of 0.25 (mg/dl) (APHIS), a risk of type I error of 5% and a power of 80%. The cumulated z-curve (blue curve) crosses the trial sequential monitoring boundary implying that there is firm evidence for a beneficial effect of 0.25 (mg/dl) decrease in serum creatinine when the cumulative meta-analysis is adjusted for multiple testing on accumulating data.



Concentration of serum bilirubin (mg/dl) is reduced in the pentoxifylline group compared to the control group (MD -1.55; 95% CI -5.10 to 2.00); this result is not statistically significant (Analysis 5.2). Trial sequential analysis of the effect of pentoxifylline on serum bilirubin in participants with alcoholic hepatitis was not plausible. The trial sequential monitoring boundary was not calculated because the available information size is too small; less than 1% of the required information size (calculated based on an intervention effect suggested by the Akriavidis 2000 trial with low risk of bias) (Figure 6). To perform trial sequential analysis when there is such a deficit of information would be meaningless, and firm evidence would not be reached.

Figure 6. Trial sequential analysis of the cumulative meta-analysis of the effect of pentoxifylline on serum bilirubin in participants with alcoholic hepatitis. The trial sequential monitoring boundary is not calculated because the actual information size is less than 1% of the information size required. This is calculated based on an intervention effect of 1.00 (mg/dl) suggested by the one trial with low risk of bias.



Liver histology and quality of life

No trials reported on liver histology nor on quality of life.

Adverse events

Typically, adverse events are less well reported than other outcome measures, so we also considered quasi-randomised studies and observational studies in the assessment of adverse events. We identified one case-controlled study (Louvet 2008); however, it did not report on adverse events. Two of the included randomised clinical trials reported on the occurrence of adverse events. McHutchison 1991 reported that the pentoxifylline group experienced significantly less renal impairment and fever, but no data were given. Only one trial gave data on the occurrence of adverse events (Akriviadis 2000).

In Akriviadis 2000 there were a total of 33 occurrences of adverse events in the pentoxifylline group compared with 15 occurrences

in the control group; the adverse events reported ranged in their seriousness (Table 3). However, these data are not reported per participant, so some participants may have experienced more than one adverse event. Therefore, these data are count data, not dichotomous data. As such, the planned meta-analysis of total adverse events was not possible.

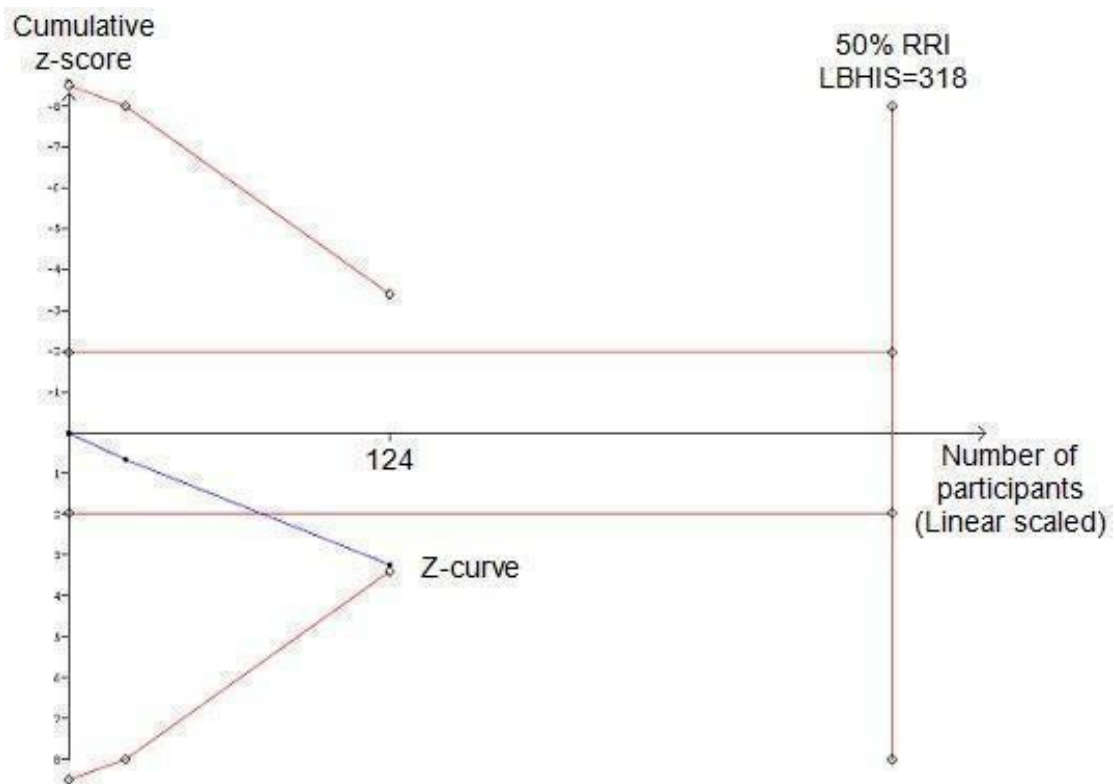
Adverse events caused more participants from the pentoxifylline group (7/50, 14%) than from the control group (1/52, 2%) to withdraw from the trial (Table 4). As these data are dichotomous, we decided to perform a post-hoc statistical analysis on the number of withdrawals due to adverse events (Table 1). Statistical significance was determined using Fisher's exact test; the result was statistically significant ($P=0.026$).

Post-hoc outcome measures, TNF levels

Meta-analysis of the data from McHutchison 1991 and Akriviadis 2000 shows a statistically significant increase in plasma TNF (tu-

mour necrosis factor) (pg/ml) in the pentoxifylline group (MD 4.04; 95% CI 1.59 to 6.48) (Analysis 6.1). Trial sequential analysis on these data does not support an increase of 4 pg/ml of TNF in the pentoxifylline group compared to control (Figure 7). Even though the z-curve (blue curve) lies in the direction of an increase in TNF in the pentoxifylline group, it does not cross the trial sequential monitoring boundary, therefore firm evidence for a 4 pg/ml increase is not reached.

Figure 7. Trial sequential analysis of the cumulative meta-analysis of the effect of pentoxifylline on levels of TNF in participants with alcoholic hepatitis. The required information size of 318 is calculated based on an intervention effect of 4.00 pg/ml, suggested by the one trial with low risk of bias (LBHIS) (Akriviadis 2000), a risk of type I error of 5% and a power of 80%. The cumulated z-curve (blue curve) does not cross the trial sequential monitoring boundary implying that there is no firm evidence for a potentially harmful effect of 4.00 pg/ml when the cumulative meta-analysis is adjusted for multiple testing on accumulating data.



DISCUSSION

There is a lack of effective treatment for alcoholic hepatitis. This systematic review examined the evidence from randomised clinical trials for the use of pentoxifylline for alcoholic hepatitis.

All-cause mortality

The data from all five included trials were analysed by meta-analysis as well as by trial sequential analysis. The meta-analysis showed that pentoxifylline reduced mortality in participants with alcoholic hepatitis; this result was statistically significant (Analysis 1.1). However, the results of the trial sequential analysis did not support the traditional meta-analysis (Figure 3). Trial sequential analysis showed that the intervention effect (z-curve, blue line) did not cross the trial sequential monitoring boundary (red curve) indicating lack of information to detect or reject a statistically significant intervention effect of 20% risk ratio reduction (RRR) (Figure 3). Trial sequential analysis is a statistical analysis that is adjusted for multiple testing on accumulating data and, therefore, is a more robust analysis than cumulative meta-analysis. As such, we lack firm evidence on the intervention effect of pentoxifylline and cannot conclude that pentoxifylline has a positive intervention effect on mortality in participants with alcoholic hepatitis. The trial sequential analysis result also indicates that in order to detect or reject with firm evidence an intervention effect of 20% risk ratio reduction, an information size of 1169 may be needed (Figure 3). Risk of bias is known to impact on the estimated intervention effect, with trials of a high risk of bias tending to overestimate the intervention effect (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008). To assess the effect of risk of bias on the analysis of all-cause mortality, the included trials were categorised as having either a high or a low risk of bias. Four of the five included trials were judged to be of high risk of bias (Figure 1). Therefore, the estimated intervention effect calculated using data from all five trials is at high risk of bias and is not a robust result.

Separate meta-analyses were conducted on the trial with a high risk of bias and on those with a low risk of bias. The meta-analysis on the high risk of bias trials showed that pentoxifylline had a non-statistically significant positive intervention effect on all-cause mortality (Analysis 1.3). Interestingly, the meta-analysis on the single trial with a low risk of bias (Akriviadis 2000) showed greatest intervention effect, a risk ratio of 0.52, and hence, the result is statistically significant (Analysis 1.3).

The trials with a high risk of bias also have very small information sizes, so their results could also be affected by random error. It is also worth noting that the control event rate in the Akriviadis 2000 trial is 48%, whereas the weighted average control event rate in all trials is 39%. A control event rate, which is close to 50%, makes it easier to detect an intervention effect. This may contribute to the explanation that the low risk of bias trial and not the high risk of bias trial estimates a greater intervention effect.

A test of interaction between high risk and low risk of bias trials did not show a significant effect between these two groups, suggesting that risk of bias did not impact on the estimated intervention effect for all-cause mortality. However, this result is limited because of the small sample sizes in each group (Altman 2003).

Basing recommendations on data from only one trial is not advisable, so the analysis of one trial with 102 participants and a low

risk of bias is not sufficient evidence on which to draw conclusions (Akriviadis 2000). This is in part because the information size is too small, which means that there is a risk of random error, ie, that the result is actually a false positive (type I error) or a false negative (type II error). As such we need at least one other trial with a low risk of bias demonstrating benefit, before any positive intervention effect can be determined.

Hepatic-related mortality

Meta-analysis showed that hepatic-related mortality (caused by hepatorenal syndrome) was reduced in the pentoxifylline group compared to the control group, and this result was statistically significant (Analysis 2.1). The result can be expressed as a reduction in the risk of hepatic-related mortality estimated to be 60%. Although the statistical heterogeneity of the analysis was high, $I^2 = 22%$, there was no discrepancy in the results using either the fixed-effect or random-effects model (Analysis 2.2). A fourth included trial reported on hepatorenal syndrome, but did not give any data; therefore, this trial has not been included in the meta-analysis (McHutchison 1991). The trial reports a statistically significant decrease in hepatorenal syndrome in the pentoxifylline group compared to control (McHutchison 1991), agreeing with the meta-analysis here.

The biochemical parameters, which indicate kidney function (blood urea nitrogen and serum creatinine), are both reduced in the pentoxifylline group compared to the control group (Table 2 and Analysis 5.1) and both results are statistically significant. The trial sequential analysis of the data on serum creatinine shows firm evidence of a decrease in serum creatinine in the pentoxifylline group compared to control. Although the prognostic role of serum creatinine for hepatorenal syndrome is widely accepted, the data presented in our review are not sufficient firm evidence to support that pentoxifylline reduces hepatorenal syndrome. The data can, however, generate the hypothesis for a randomised clinical trial to investigate the effect of pentoxifylline on hepatorenal syndrome and examine the validity of serum creatinine as a surrogate marker for the potential effect of pentoxifylline on hepatorenal syndrome. Trial sequential analysis was also performed on the data for hepatic-related mortality (all occurrences caused by hepatorenal syndrome) (Figure 4). The trial sequential analysis showed that the z-curve (blue curve) does not cross the trial sequential monitoring boundary (red curve), implying that there is no firm evidence for an effect of 20% risk ratio reduction (RRR). The results of the trial sequential analysis does not support that there is firm evidence for the intervention effect suggested by the meta-analysis; however, it is a more robust result because it is adjusted for multiple testing on accumulating data, so reduces the risk of random error.

The trial sequential analysis was adjusted for heterogeneity, resulting in a larger required information size than currently accrued. The total number of participants contributing to these analyses is only 182, whereas the required information size is 1636 partici-

pants. This highlights the risk of random error in the results from the meta-analysis, which only includes data from 182 participants. There is no firm evidence that pentoxifylline reduces hepatorenal syndrome in participants with alcoholic hepatitis (Figure 4).

Adverse events

Only one trial provided data on adverse events (Akriviadis 2000); there were a total of 33 occurrences of adverse events in the pentoxifylline group compared to 15 occurrences in the control group. The adverse events ranged in their seriousness (Table 3). No pre-planned analysis could be performed on these data as they are count data. However, we did perform post-hoc analysis on the number of participants who withdrew from the trial due to adverse events as these data are dichotomous (Table 1). The data show a statistically significant increase in the number of withdrawals due to adverse events in the pentoxifylline group than in the control group (Table 1). Post-hoc analyses can be biased, as they may be driven by the statistical significance of the results. The reason for our post-hoc analysis was that the data in the Akriviadis 2000 trial were dichotomous, related to adverse events, and lent themselves to our statistical analysis.

There were 13 reports of epigastric discomfort or pain with or without vomiting in the pentoxifylline group and five reports in the control group (Table 3). These data may suggest that pentoxifylline causes increased epigastric discomfort or pain without vomiting in participants with alcoholic hepatitis. This is in agreement with what is known regarding xanthine derivatives (of which pentoxifylline is one), ie, that they cause adverse effects such as epigastric pain and other gastric problems (Patient 2008).

The total number of occurrences of adverse events, the number of withdrawals due to adverse events, and the reports of epigastric pain, all indicate an increase of serious and non-serious adverse events in the pentoxifylline group compared to the control group. The main caveat to be entered with respect to these adverse event data is that only one trial reported on adverse events. Only a trend in increased adverse events in the pentoxifylline group can be noted. Data on adverse events from the other trials are necessary to evaluate any possible harmful effect of pentoxifylline in participants with alcoholic hepatitis.

Tumour necrosis factor

A caveat should be entered here, as these analyses were not pre-defined in the protocol, ie, it was a post-hoc analysis. We feel that analysing TNF levels is a valid outcome measure as pentoxifylline is proposed to be an inhibitor of TNF ligand gene transcription (Strieter 1988), although this is currently under debate (Lucey 2009).

Meta-analysis of the data from McHutchison 1991 and Akriviadis 2000 shows a statistically significant increase in plasma TNF (tumour necrosis factor) concentration in the pentoxifylline group (Analysis 6.1). Trial sequential analysis on these data also indicates

that TNF concentration is higher in the pentoxifylline group compared to control, but the trial sequential monitoring boundary is not crossed, so the evidence is not firm (Figure 6). The direction of these results seems to be in contrast to the proposed TNF-inhibitory properties of pentoxifylline. An increase of 4 pg/ml of TNF indicates the activation of a stress response, but this may not be clinically significant and cannot be used as a clear surrogate outcome for either benefit nor harm. Furthermore, two caveats should be entered here, firstly, the data from the Akriviadis 2000 trial are not clearly reported. Neither the raw data, nor the unit of standard error were reported. Secondly, in the McHutchison 1991 trial report, there was a baseline imbalance in TNF levels, with a higher baseline level in the pentoxifylline group. No other laboratory parameters had a baseline imbalance, suggesting that randomisation had been successfully performed and that TNF levels may have been unequal due to chance alone. The difference in the TNF levels before and after the pentoxifylline regimen showed a greater increase in TNF levels in the control group than the pentoxifylline group which suggests that pentoxifylline actually suppressed an increase in TNF levels. In light of such inaccuracies, we do not make conclusions about the effect of pentoxifylline on TNF levels.

Limitations of this review

The limitations of this review include the high proportion of trials with a high risk of bias. Of the five included trials, four were assessed as having a high risk of bias (Figure 1). As such, the statistical analyses on these data are based primarily on high risk of bias trials (Figure 2). Assigning a risk of bias to a randomised clinical trial follows a judgement based on the information available from the publication. The four high risk of bias trials were published as abstracts only; therefore, the judgement is primarily on how well the trial was reported rather than a judgement of the design and conduct of the trial itself. A more detailed description of these trials (possibly a full text publication) may lead to future re-classification of their risk of bias.

Another limitation of this review is that all five included trials had a small sample size, with an average of 67 participants with alcoholic hepatitis. Small trials have less power, meaning that there is less chance of detecting a small but true effect as statistically significant (Kjaergard 2001). Small trials are also prone to increased risk of random error, and meta-analysis, which combines data from small trials may yield false results (Brok 2008). This is one reason that we also analysed the data using trial sequential analysis.

Trial sequential analysis

Random error is the probability of observing a result by chance. Type I error is the risk of observing false positive results and type II error is the risk of observing false negative results. Random error can lead to false conclusions about the intervention effect.

Random error can occur in data from individual trials and in data from meta-analysis. The risk of random error is higher when data come from small information sizes (or 'sample sizes' for individual trials), so information sizes need to be sufficiently large in order to reduce the risk of random error and increase the chance of observing a true intervention effect (Brok 2008; Wetterslev 2008). The risk of random error in meta-analysis is potentially further exacerbated when one performs, formally or informally, statistical analyses repeatedly as new trials provide additional data; this occurs whenever new trial data become available and when meta-analyses are updated. The benefit of using trial sequential analysis is that it controls for such an exacerbation of random error, which a traditional cumulative meta-analysis does not (Brok 2008a).

Elements of a trial sequential analysis include an information size, trial sequential monitoring boundaries (red curves), and a cumulative z-curve (blue curve). The information size is the number of participants needed in the analysis to detect or reject a certain intervention effect and is calculated based on an a priori, realistic intervention effect (here 20% risk ratio reduction) and a risk of type I error of 5% and a power of 80%. The trial sequential monitoring boundaries are based on the required information size and on the a priori intervention effect (Thorlund 2008). The cumulative z-curve (blue curve) represents the estimated intervention effect generated from the data from the trials. If the cumulative z-curve (blue curve) crosses the trial sequential monitoring boundary (red curve), then a sufficient level of evidence is reached and no further trials are needed. However, if the z-curve does not cross the boundary, then there is insufficient evidence to reach a conclusion, which is what we see in this review for the outcome measures all-cause mortality and hepatorenal syndrome (Brok 2008a). Additionally, trial sequential analysis provides us with important information regarding the need for additional trials and the required information size.

In this Cochrane review we used trial sequential analysis to analyse data on all-cause mortality and on hepatorenal syndrome. We applied trial sequential monitoring boundaries according to an information size suggested by an a priori risk ratio reduction (RRR) of 20% (Thorlund 2008). The current information size is 336 participants from all five trials, with 102 participants coming from the single low risk of bias trial. At least 800 participants may be needed in order to detect or reject a risk ratio reduction (RRR) of 20% in the analyses. Therefore, our current analyses, being mere interim-analyses in this perspective, cannot reach firm conclusions. The main findings of this Cochrane systematic review are that there is a trend in reduction of all-cause mortality, reduction of hepatorenal syndrome, and an increase in adverse events in par-

ticipants who received pentoxifylline; but firm evidence for this is still absent. Data from low risk of bias trials, providing a large information size, are needed in order to draw firm conclusions from the data. Such data can then be added to the trial sequential analyses. Trial sequential analysis controls for the worst case scenario of increased risk of random error whenever you add new trial data to the existing data for an updated analysis.

One trial that was identified in our search of clinicaltrials.gov is classified in this review as an ongoing study (NCT00205049). The final collection of primary outcome measures was July 2008; our search strategy was performed in August 2009 and did not identify a corresponding publication. We await the publication of these results in order to update our analysis.

AUTHORS' CONCLUSIONS

Implications for practice

Treatment of alcoholic hepatitis with pentoxifylline can neither be supported nor rejected based on the best current evidence available.

Implications for research

Randomised clinical trials, which assess both benefits and harms of pentoxifylline in alcoholic hepatitis, with large sample sizes, and minimised risk of bias are needed. Alcoholic hepatitis is a relatively rare disease, so multi-national, multi-centre trials would be effective for participant recruitment and generalisability. The resulting data can then be added to the trial sequential analyses performed here, in order to assess the intervention effect whilst controlling for the risk of random error.

ACKNOWLEDGEMENTS

We thank the participants and investigators who took part in the clinical trials. We thank Dimitrinka Nikolova for her expertise and guidance. We thank Nader Salas and Styrbjörn Birch for invaluable IT assistance. Thank you to Didier Lebrec for clarifying information relating to the randomised clinical trial he participated in.

Peer Reviewers: H Tilg, Austria, IN Guha, S Stewart, UK.

Contact Editor: Rosa Simonetti, Italy.

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Akriviadis 2000

Methods	<p>Trial design: randomised, double-blind, parallel design trial.</p> <p>Language: English.</p> <p>Type of publication: journal article.</p> <p>Year of trial: 1992 to 1997.</p>
Participants	<p>Country: USA.</p> <p>Number of participants: 102. Fifty received pentoxifylline, 52 received placebo.</p> <p>Sex ratio: 75M, 26W (74% M).</p> <p>Mean age: 41 years.</p> <p>Duration of alcoholic hepatitis: not specified.</p> <p>Inclusion criteria: jaundice, Maddrey discriminant factor more than or equal to 32 and one or more of: palpable tender hepatomegaly, fever, leukocytosis (white blood cells greater than 12,000/mm³ with predominantly neutrophilic differentiation), hepatic encephalopathy, hepatic systolic bruit. No histological diagnosis.</p> <p>Exclusion criteria: concomitant bacterial infections, active gastrointestinal haemorrhage, severe cardiovascular or pulmonary disease, clinical evidence of alcoholic cirrhosis, decreasing serum bilirubin values or rapid improvement of other liver test results over the first post admission days</p>
Interventions	<p>Intervention: pentoxifylline 400 mg three times a day, orally, 28 days.</p> <p>Control: placebo, vitamin B12 500 or 1000 micro g, same regimen.</p> <p>Co-interventions: none specified, we assume that all participants received standard treatments for liver disease and any co-morbidities</p>
Outcomes	<p>Primary outcome measure(s): 28-day survival and progression to hepatorenal syndrome. 12/50 (24%) in pentoxifylline group died. 24/52 (46%) in control group died. Hepatorenal syndrome developed in 6/50 (21%) in pentoxifylline group and 22/52 (42%) in control group.</p> <p>Secondary outcome measure(s): laboratory parameters, serum TNF levels and development of clinical complications of liver disease. In the pentoxifylline group 15 experienced hepatic-related morbidity. In the control group 21 experienced hepatic-related morbidity.</p> <p>Adverse events: 33 adverse events occurred in the pentoxifylline group, 15 occurred in the control group.</p> <p>Period of follow-up: 6 month follow-up of survival data.</p>
Notes	<p>Compliance with the intervention regimen was lower in the pentoxifylline group. In the pentoxifylline group 12 discontinued treatment, one dropped out and was not included in the analysis, seven withdrew due to adverse events, four did not adhere to the regimen and/or all the follow-up appointments. In the control group four discontinued treatment, one due to adverse events, and three did not adhere to the regimen and/or all the follow-up appointments</p> <p>In March 2008 a letter was written to Akriviadis for clarification of sample size calculation, pre-published protocol, and trial sponsorship. No response has so far been received</p>

Akriviadis 2000 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	An independent person randomly selected sealed envelopes.
Allocation concealment?	Low risk	Drugs were coded and distributed by hospital pharmacy; tablets were enclosed in opaque capsules
Blinding? All outcomes	Low risk	Placebo was packaged in identical opaque capsules; placebo had similar size and appearance to treatment
Incomplete outcome data addressed? All outcomes	Low risk	The number and reasons for withdrawals were given and six-month survival data was obtained for all
Free of selective reporting?	Low risk	Predefined, clinically relevant, and expected outcomes are reported
Free of other bias?	Unclear risk	Intention-to-treat analysis was not performed; one drop-out was not included in the analysis. Sample size calculation was not reported

Lebrec 2007

Methods	Trial design: randomised, double-blind, parallel design trial. Language: English. Type of publication: abstract. Year of trial: not reported
Participants	Country: France. Number of participants: 332 with Child-Pugh C cirrhosis without hepatocellular carcinoma, with a subgroup of 132 participants with severe acute alcoholic hepatitis. Sex ratio: not reported. Mean age: not reported. Duration of alcoholic hepatitis: not specified. Inclusion criteria: Child-Pugh C cirrhosis. Exclusion criteria: advanced hepatocellular carcinoma.
Interventions	Intervention: pentoxifylline 400 mg three times a day, orally, duration not described. Control: placebo. Co-interventions: all participants received standard therapy for their liver disease and any co-morbidity

Outcomes	<p>Primary outcome measure(s): death at 2 months. In the subgroup with severe alcoholic hepatitis of those who received pentoxifylline 14% died, and of those who received control 46% died within 2 months. Secondary outcome measure(s): death at 6 months. In the subgroup with severe alcoholic hepatitis of those who received pentoxifylline 27% died, and of those who received control 31% died within 2 months. Personal communication with the coordinating investigator Didier Lebrec tells us that from the subgroup of participants with alcoholic hepatitis, 19 participants in each group died. Meaning 19/71 died in the pentoxifylline group and 19/61 died in the control group. Adverse events: no differences. Period of follow-up: 6 months.</p>	
Notes	<p>The numbers of participants randomised to either pentoxifylline or placebo in the subgroup with severe alcoholic hepatitis are not given. The outcome measures for these participants are reported as percentages In March 2008 a letter was written and we telephoned Didier Lebrec where he kindly clarified the number of participants with alcoholic hepatitis in each intervention group and the number of those participants who died</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Centrally controlled, computer generated randomisation sequence
Allocation concealment?	Low risk	Centrally controlled, computer generated randomisation sequence
Blinding? All outcomes	Low risk	Described as double-blind and placebo used.
Incomplete outcome data addressed? All outcomes	Unclear risk	No withdrawals or drop-outs were reported.
Free of selective reporting?	Unclear risk	The trial was registered on clinical trials.gov (NCT00162552) which listed out pre-defined outcome measures: primary outcome measure: survival rate at 2 months. Secondary outcome measures: survival rate at 6 months; number of patient with liver transplantation; complications (bacterial infection, renal insufficiency, hepatic encephalopathy, gastrointestinal bleeding); fibrotest and acutest at 2 and 6 months; TNF alpha and IL6 plasma concentration at 2 and 6 months. Only 2 and 6 month mortality was reported in this publication

Lebrec 2007 (Continued)

Free of other bias?	Unclear risk	Sample size calculation was reported on clinicaltrials.gov, calculated for participants with severe cirrhosis, data analysed from participants with alcoholic hepatitis was a subgroup analysis
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McHutchison 1991

Methods	Trial design: randomised, parallel design pilot trial. Language: English. Type of publication: abstract. Year of trial: not reported.	
Participants	Country: USA. Number of participants: 22. Twelve received pentoxifylline, 10 received standard treatment. Sex ratio: not reported. Mean age: not reported. Duration of alcoholic hepatitis: not specified. Inclusion criteria: severe alcoholic hepatitis as defined by bilirubin greater than or equal to 10 mg/dl, prothrombin ratio less than or equal to 12000 mm ³ , tender hepatomegaly, fever greater than or equal to 100 °F. Exclusion criteria: active infection.	
Interventions	Intervention: pentoxifylline 1200 mg once a day, orally, 10 days. Control: standard treatment. Co-interventions: none specified, we assume that all participants received standard treatments for liver disease and any co-morbidities	
Outcomes	Primary outcome measure(s): biochemical parameters and plasma TNF levels. Renal impairment, fever and mortality were also recorded. Biochemical parameters are reported as means for each group. "Significantly less renal impairment and fever" in the pentoxifylline group, data not given. For mortality, the article states: "Thirty day mortality was higher in controls compared to treated patients (1 vs 3, p = not significant)", meaning that one participant in the pentoxifylline group died and three in the control group died Secondary outcome measure(s): not specified. Adverse events: not reported. Period of follow-up: 10 days after treatment follow-up of biochemical data, 30 days after treatment follow-up of survival data	
Notes	In March 2008 a letter was written to McHutchinson for clarification of: what exactly constituted 'standard treatment'; if there were any co-interventions; allocation sequence generation; allocation concealment; blinding; loss to follow-up; outcome measure data; sample size calculation; pre-published protocol; and trial sponsorship. The letter was later returned to sender	

Risk of bias

McHutchison 1991 (Continued)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, but the method was not described
Allocation concealment?	Unclear risk	No allocation concealment method was described
Blinding? All outcomes	Unclear risk	Described as blind, but the method was not described.
Incomplete outcome data addressed? All outcomes	Unclear risk	No withdrawals were reported.
Free of selective reporting?	High risk	Hepatic-related morbidity was not reported. Renal impairment, fever, and mortality were not pre-defined as primary outcomes
Free of other bias?	Unclear risk	Intention-to-treat analysis was not reported. Sample size calculation not reported. Risk of multiple publication bias, as this pilot trial led to the trial of Akiviadis et al 2000

Paladugu 2006

Methods	Trial design: randomised, parallel design trial. Language: English. Type of publication: abstract. Year of trial: not reported.
Participants	Country: India. Number of participants: 30. Fourteen participants received pentoxifylline, 16 participants received placebo. Sex ratio: 30M, 0W (100% M). Mean age: 47 years. Duration of alcoholic hepatitis: not specified. Inclusion criteria: severe alcoholic hepatitis as defined by Maddrey discriminant factor more than or equal to 32 or hepatic encephalopathy. Exclusion criteria: not specified.
Interventions	Intervention: dose and regimen of pentoxifylline not described, duration 4 weeks. Control: placebo. Co-interventions: none specified, we assume that all participants received standard treatments for liver disease and any co-morbidities
Outcomes	Primary outcome measure(s): end-of-study survival or hepatorenal syndrome. 4/14 in the pentoxifylline group died, and 7/16 in the control group died. Of those who died,

Paladugu 2006 (Continued)

	<p>hepatorenal syndrome occurred in 2/4 of the pentoxifylline group and 6/7 of the control group. Secondary outcome measure(s): not specified. TNF levels were also reported, with no difference between groups at then end of the trial. Adverse events: not reported. Period of follow-up: during 4 week trial only.</p>	
Notes	<p>In March 2008 a letter was written to Paladugu for clarification of: sequence generation; allocation concealment; blinding; loss to follow-up; outcome measure data; sample size calculation; pre-published protocol; and trial sponsorship. No response has so far been received</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, but the method was not described.
Allocation concealment?	Unclear risk	Described as randomised, but the method was not described.
Blinding? All outcomes	Unclear risk	Not described as blind, but described as placebo controlled.
Incomplete outcome data addressed? All outcomes	Unclear risk	No withdrawals were reported.
Free of selective reporting?	Low risk	Reporting on mortality, hepatorenal syndrome and TNF levels was according to objectives and pre-defined outcome measures
Free of other bias?	Unclear risk	Sample size calculation was not reported.

Sidhu 2006

Methods	<p>Trial design: randomised, parallel design trial. Language: English. Type of publication: abstract. Year of trial: not reported.</p>
Participants	<p>Country: India. Number of participants: 50. Twentyfive participants received pentoxifylline, 25 participants received placebo. Sex ratio: 50M, 0W (100% M). Mean age: not reported. Duration of alcoholic hepatitis: not specified. Inclusion criteria: severe alcoholic hepatitis as defined by Maddrey discriminant factor more than or equal to 32.</p>

	Exclusion criteria: not specified.	
Interventions	Intervention: pentoxifylline 400 mg three times a day, orally, 28 days. Control: placebo. Co-interventions: none specified, we assume that all participants received standard treatments for liver disease and any co-morbidities	
Outcomes	Primary outcome measure(s): short-term survival. 6/25 in the pentoxifylline group died, and 10/25 in the control group died. Of those who died, hepatorenal syndrome occurred in 5/25 of the pentoxifylline group and 6/25 of the control group. Secondary outcome measure(s): laboratory parameters. Pentoxifylline treated group showed "significant reduction in Prothrombin Time, DF and TNF level in serum". Adverse events: not reported. Period of follow-up: during 28 day trial only.	
Notes	No raw data was given for the laboratory variables.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, but the method was not described.
Allocation concealment?	Unclear risk	Described as randomised, but the method was not described.
Blinding? All outcomes	Low risk	Described as double-blind and placebo controlled.
Incomplete outcome data addressed? All outcomes	Unclear risk	No withdrawals were reported.
Free of selective reporting?	Low risk	Outcome measures were pre-defined and reported, ie, short-term survival and laboratory parameters. Hepatic-related morbidity was reported on
Free of other bias?	Unclear risk	Sample size calculation was not reported.

M = men.
W = women.
g = gram.
mg = milligram.
mm³ = millimetre cubed.
DF = discriminant factor
vs = versus.

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

Study	Reason for exclusion
Austin 2004	Participants had alcoholic cirrhosis, not alcoholic hepatitis
Cholongitas 2001	Comment on Akriviadis 2000 .
Fernández-Rodríguez 2008	Participants had alcoholic cirrhosis, there was no data presented for participants with alcoholic hepatitis
Lee 2006	Participants had non-alcoholic steatohepatitis.
Louvet 2008	Case-controlled study. Twenty-nine participants took pentoxifylline
Verma 2006	Retrospective, participants not randomised.
Watson 2008	Retrospective, participants not randomised.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[NCT00205049](#)

Methods	Randomised, double-blind, placebo control, phase III.
Participants	Alcoholic hepatitis, in adults and seniors.
Interventions	Pentoxifylline.
Outcomes	Not specified.
Notes	Sponsor is the University of Wisconsin, Madison. Completion date is July 2007

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

[NCT00388323](#)

Trial name or title	Adipose tissue involvement in alcohol-induced liver inflammation in human: study of pro- and anti-inflammatory cytokines and adipokines
Methods	Observational, prospective study, phase III.
Participants	Alcoholic hepatitis or alcoholic cirrhosis in adults and seniors
Interventions	Not specified.

NCT00388323 (Continued)

Outcomes	Not specified.
Starting date	November 2006.
Contact information	http://ClinicalTrials.gov/show/NCT00388323
Notes	Sponsor is Assistance Publique Hôpitaux de Paris. Completion date is October 2008

DATA AND ANALYSES

Comparison 1. All-cause mortality, pentoxifylline versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality using the fixed effect model	5	336	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.89]
2 Mortality using the random effects model	5	336	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.47, 0.90]
3 Mortality according to risk of bias	5	336	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.89]
3.1 Low risk of bias	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.29, 0.92]
3.2 High risk of bias	4	234	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.48, 1.07]

Comparison 2. Hepatic-related mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hepatic-related mortality using fixed-effect model	3	182	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.22, 0.71]
2 Hepatic-related mortality using the random-effects model	3	182	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.22, 0.85]

Comparison 3. Sensitivity analysis, all-cause mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5	672	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.52, 0.82]
1.1 Mortality, sensitivity analysis with all missing mortality data survived	5	336	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.89]
1.2 Mortality, sensitivity analysis with all missing mortality data died	5	336	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.48, 0.91]

Comparison 4. Hepatic-related morbidity, pentoxifylline versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Variceal bleeding	2	132	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.42, 11.32]

Comparison 5. Biochemical parameters, pentoxifylline versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum creatinine	2	124	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-1.14, -0.87]
2 Serum bilirubin	2	124	Mean Difference (IV, Fixed, 95% CI)	-1.55 [-5.10, 2.00]

Comparison 6. Post-hoc outcome measures, TNF levels

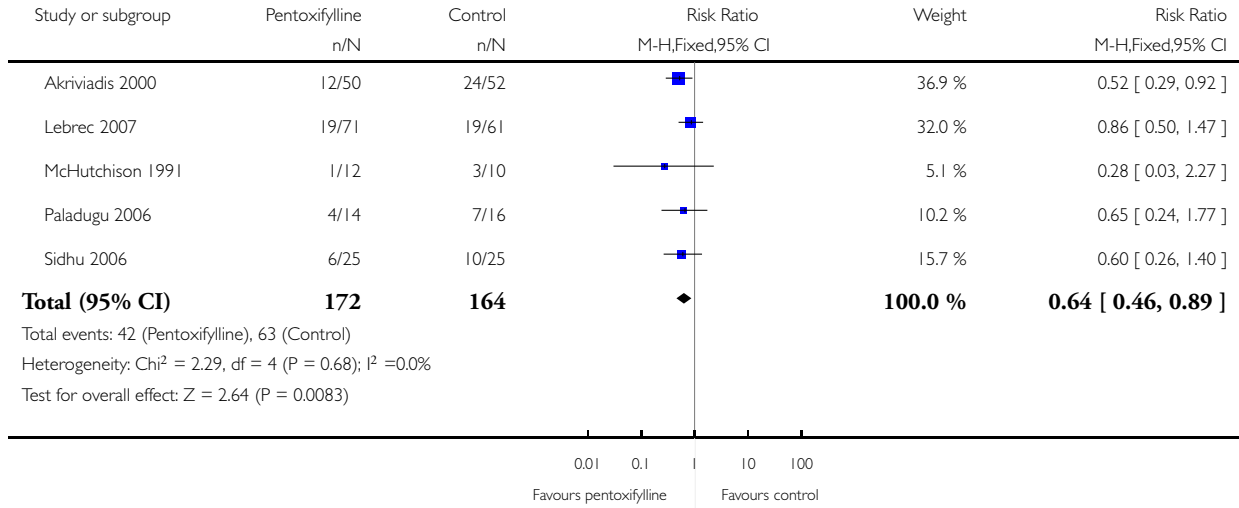
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tumour necrosis factor	2	124	Mean Difference (IV, Fixed, 95% CI)	4.04 [1.59, 6.48]

Analysis 1.1. Comparison 1 All-cause mortality, pentoxifylline versus control, Outcome 1 Mortality using the fixed effect model.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 1 All-cause mortality, pentoxifylline versus control

Outcome: 1 Mortality using the fixed effect model

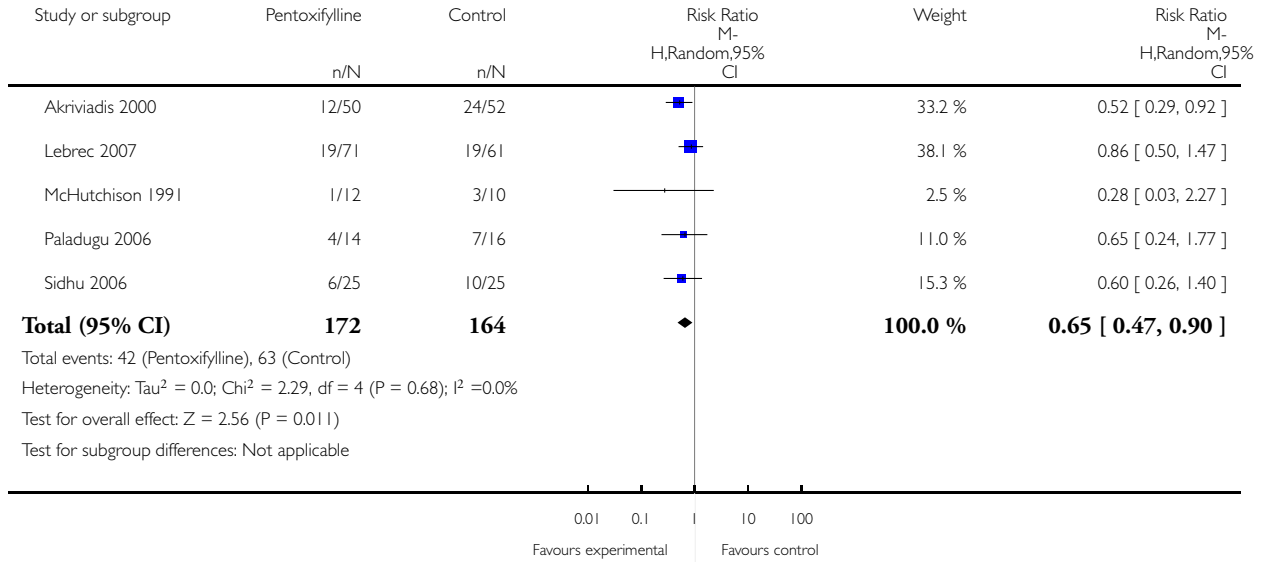


Analysis 1.2. Comparison 1 All-cause mortality, pentoxifylline versus control, Outcome 2 Mortality using the random effects model.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 1 All-cause mortality, pentoxifylline versus control

Outcome: 2 Mortality using the random effects model

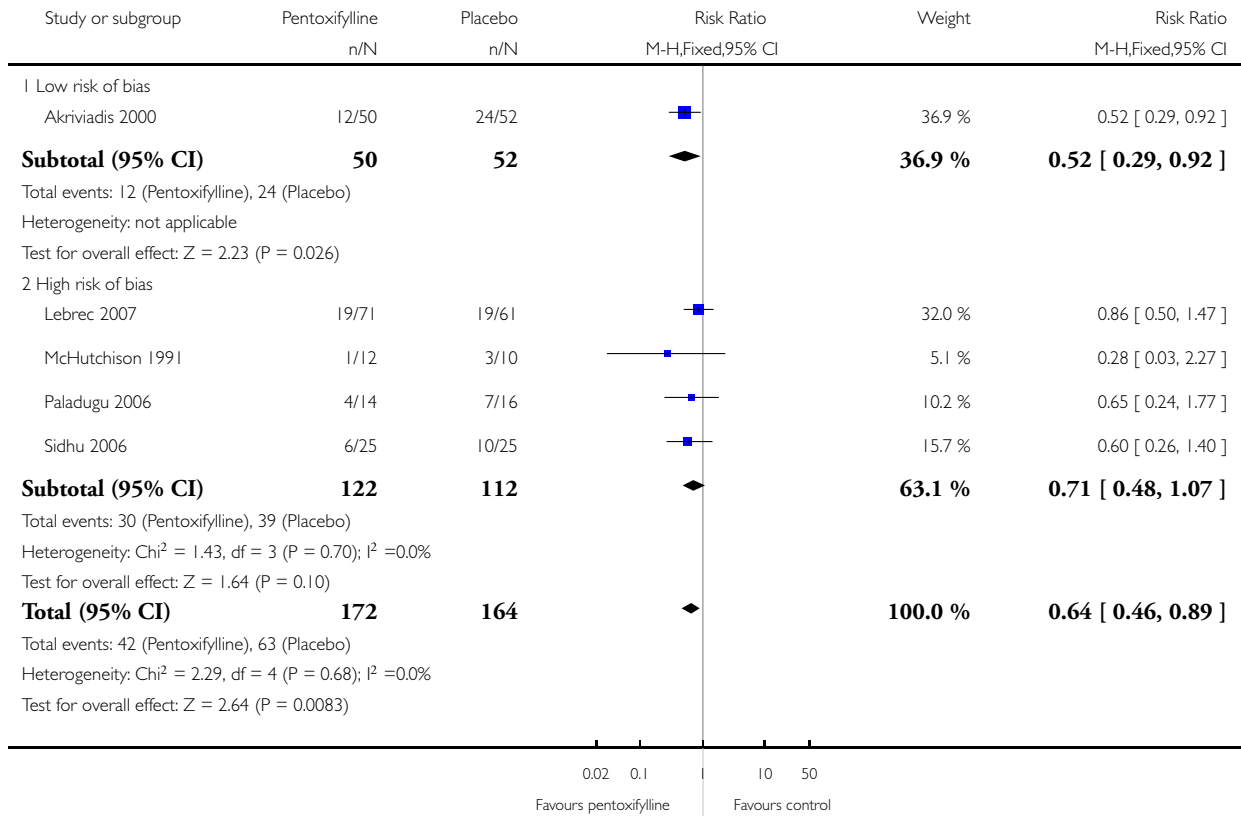


Analysis 1.3. Comparison 1 All-cause mortality, pentoxifylline versus control, Outcome 3 Mortality according to risk of bias.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 1 All-cause mortality, pentoxifylline versus control

Outcome: 3 Mortality according to risk of bias

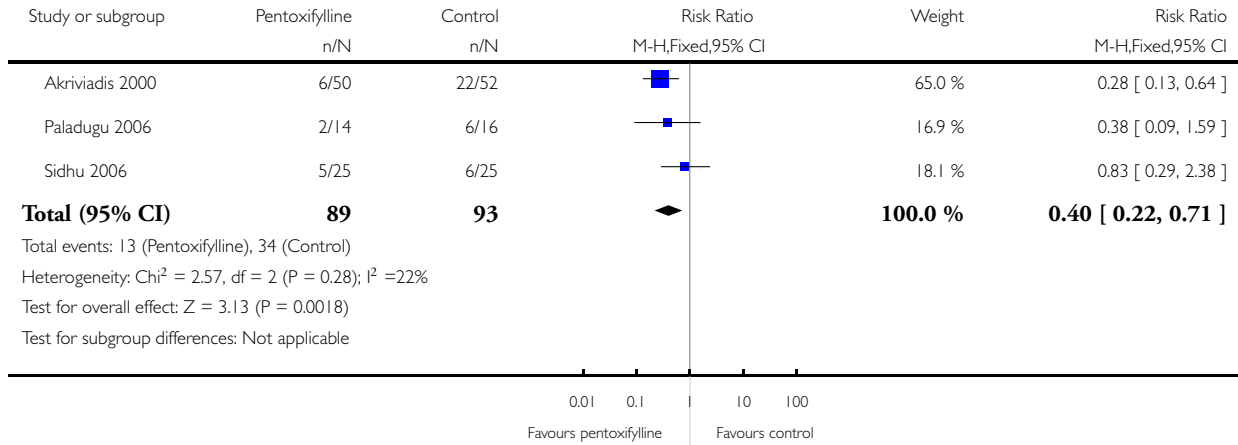


Analysis 2.1. Comparison 2 Hepatic-related mortality, Outcome 1 Hepatic-related mortality using fixed-effect model.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 2 Hepatic-related mortality

Outcome: 1 Hepatic-related mortality using fixed-effect model

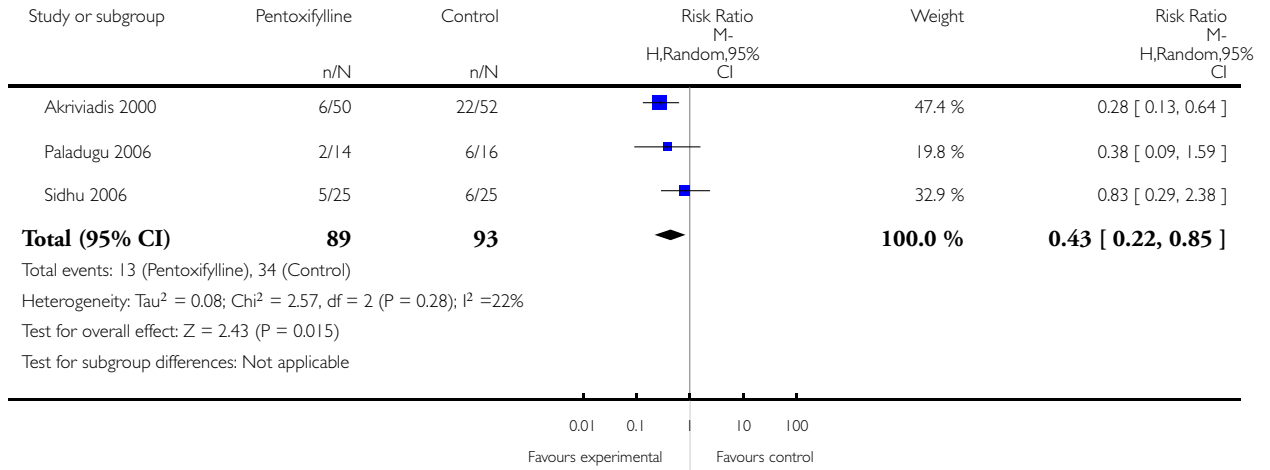


Analysis 2.2. Comparison 2 Hepatic-related mortality, Outcome 2 Hepatic-related mortality using the random-effects model.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 2 Hepatic-related mortality

Outcome: 2 Hepatic-related mortality using the random-effects model

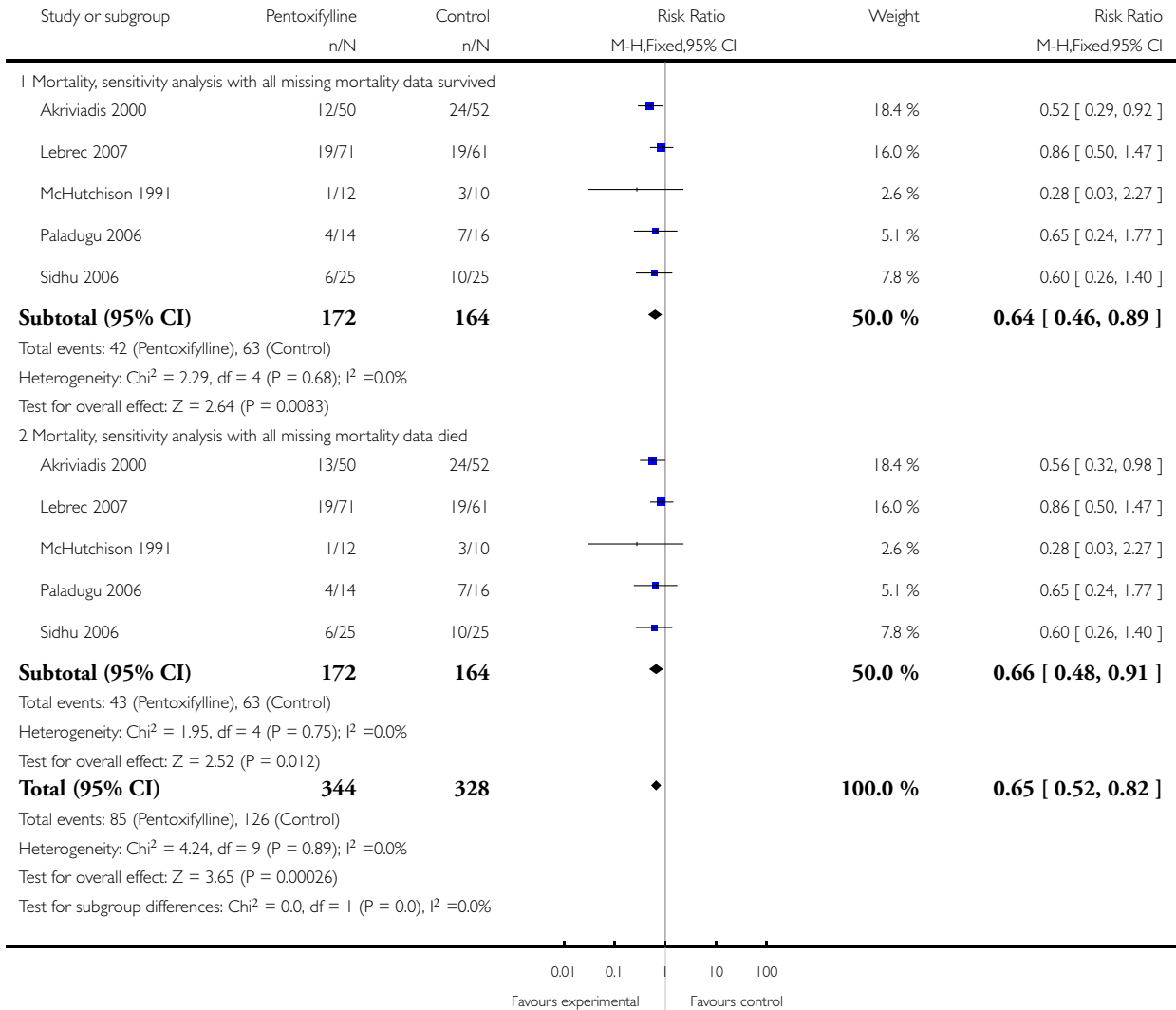


Analysis 3.1. Comparison 3 Sensitivity analysis, all-cause mortality, Outcome 1 Mortality.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 3 Sensitivity analysis, all-cause mortality

Outcome: 1 Mortality

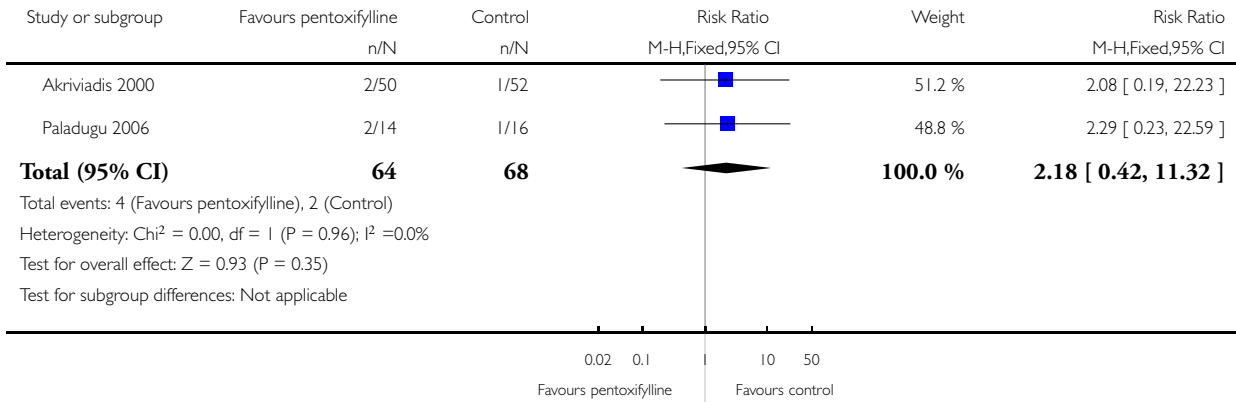


Analysis 4.1. Comparison 4 Hepatic-related morbidity, pentoxifylline versus control, Outcome 1 Variceal bleeding.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 4 Hepatic-related morbidity, pentoxifylline versus control

Outcome: 1 Variceal bleeding

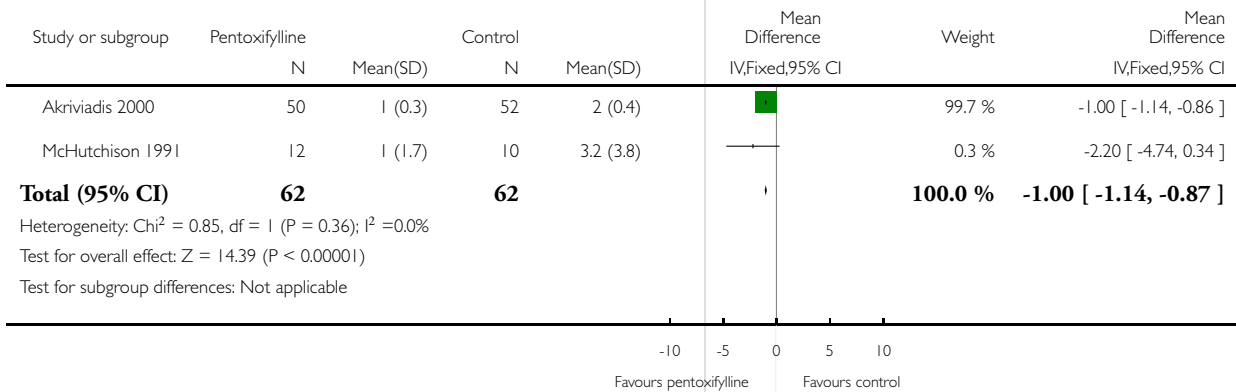


Analysis 5.1. Comparison 5 Biochemical parameters, pentoxifylline versus control, Outcome 1 Serum creatinine.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 5 Biochemical parameters, pentoxifylline versus control

Outcome: 1 Serum creatinine

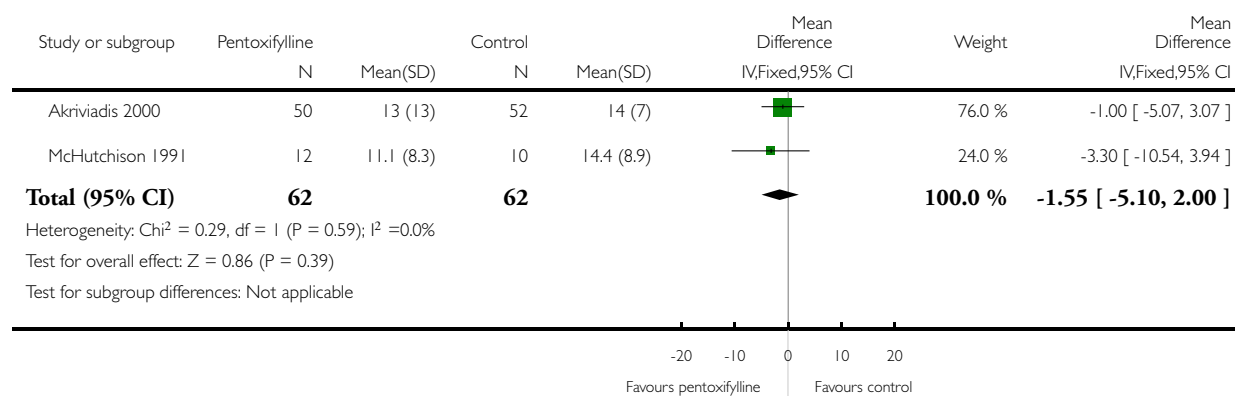


Analysis 5.2. Comparison 5 Biochemical parameters, pentoxifylline versus control, Outcome 2 Serum bilirubin.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 5 Biochemical parameters, pentoxifylline versus control

Outcome: 2 Serum bilirubin

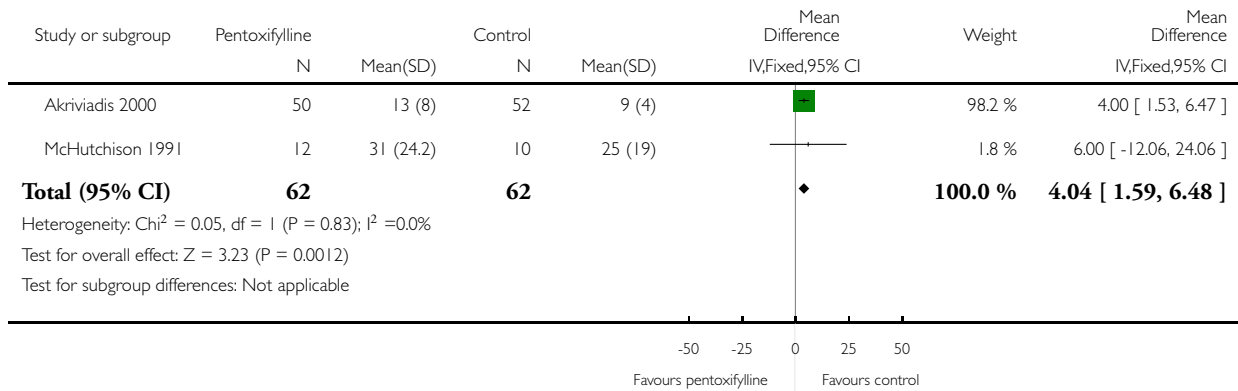


Analysis 6.1. Comparison 6 Post-hoc outcome measures, TNF levels, Outcome 1 Tumour necrosis factor.

Review: Pentoxifylline for alcoholic hepatitis

Comparison: 6 Post-hoc outcome measures, TNF levels

Outcome: 1 Tumour necrosis factor



ADDITIONAL TABLES

Table 1. Fisher's exact test

Outcome measure	Type of data	Pentoxifylline group	Control group	Statistical test	P value
Hepatic encephalopathy	Dichotomous	9/50 (18%)	13/52 (25%)	Fisher's exact test	0.133
Withdrawals due to adverse events	Dichotomous	7/50 (14%)	1/52 (2%)	Fisher's exact test	0.026

Table 2. Student's t-test

Outcome measure	Type of data	Pentoxifylline group	Control group	Statistical test	T value	P value
Blood urea nitrogen	Continuous	Mean 23 SD 28	Mean 38 SD 36	Student's T test	2.3426	0.021131
Prothrombin time	Continuous	Mean 5 SD 3	Mean 5 SD 2	Student's T test	0	1

Table 3. Adverse events reported in Akriviadis 2000

Occurrence of adverse event as reported by Akriviadis et al	Pentoxifylline	Control
Transient diarrhoea	4	2
Epigastric discomfort or pain with or without vomiting	13	5
Severe gastrointestinal symptoms and headache	3	0
Diarrhoea	1	0
Epigastric pain	1	0
Severe headache	1	0
Generalised skin rash	1	0
Headache and gastrointestinal symptoms	0	1
Urinary tract infection	1	0
Spontaneous bacterial peritonitis	3	4
Cryptococcal septicaemia	1	0
Bronchopneumonia	1	0
Pneumonia	0	1
Staphylococcal bacteraemia	0	1
Necrotising pancreatitis	0	1
Intracranial bleeding	1	0
Vaginal bleeding	1	0
Posttraumatic epidural haematoma	1	0
Total	33	15

Table 4. Lost to follow-up reported in Akriviadis 2000

Reason for loss to follow-up	Pentoxifylline	Control	Data collected
Participant dropped out	1	0	None, participant excluded from analysis.
Incomplete regimen and/or incomplete follow-up appointment	4	3	No data collected due to missed appointments, but mortality at 2 and 6 months follow-up was assessed
Treatment withdrawal due to adverse events	7	1	Adverse events and mortality at 2 and 6 months follow-up were assessed
Total	12	4	

APPENDICES

Appendix I. Search strategies

Database	Search performed	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	August 2009.	("Pentoxifyllin*" or "pentoxiphyllin*" or pentoxifyllin* or pentoxiphyllin* or artal or pentoxin or trental or pentoxil) and "alcohol*"
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Issue 3, 2009.	#1 MeSH descriptor Pentoxifylline explode all trees #2 (pentoxifyllin* or pentoxiphyllin* or artal or pentoxin or trental or pentoxil) #3 (#1 OR #2) #4 MeSH descriptor Hepatitis, Alcoholic explode all trees #5 MeSH descriptor Liver Diseases, Alcoholic explode all trees #6 (alcoholic liver disease) or (alcoholic hepatitis) #7 (#4 OR #5 OR #6) #8 (#3 AND #7)
MEDLINE (Ovid SP)	1950 to August 2009.	#1 pentoxifyllin* or pentoxiphyllin* or artal or pentoxin or trental or pentoxil #2 explode "Pentoxifylline"/ all subheadings #3 #1 or #2 #4 explode "Liver-Diseases-Alcoholic"/ all subheadings #5 explode "Hepatitis-Alcoholic"/ all subheadings #6 alcoholic hepatitis or alcoholic liver disease

(Continued)

		#7 #4 or #5 or #6 #8 #3 and #7 #9 random* or placebo* or blind* or meta-analys* or prospective or retrospective or observation* or series or cohort or case or control* or group* or stud* or trial* #10 #8 and #9
EMBASE (Ovid SP)	1980 to August 2009.	#1 pentoxifyllin* or pentoxiphyllin* or artal or pentoxin or trental or pentoxil #2 explode "pentoxifylline"/ all subheadings #3 #1 or #2 #4 explode "alcohol-liver-disease"/ all subheadings #5 alcoholic hepatitis or alcoholic liver disease #6 #4 or #5 #7 #3 and #6 #8 random* or placebo* or blind* or meta-analys* or prospective or retrospective or observation* or series or cohort or case or control* or group* or stud* or trial* #9 #7 and #8
Science Citation Index EXPANDED (http://apps.isiknowledge.com)	1945 to August 2009.	#6 #4 and #5 #5 TS=(random* or placebo* or blind* or meta-analys* or prospective or retrospective or observation* or series or cohort or case or control* or group* or stud* or trial*) #4 #3 not TS=animal* #3 #1 and #2 #2 TS=("alcohol* liver disease" or "alcoholic hepatitis") #1 TS=(pentoxifyllin* or pentoxiphyllin* or artal or pentoxin or trental or pentoxil)
LILACS (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/)	1982 to August 2009.	Pentoxi*yllin* AND alcohol*
ClinicalTrials.gov (http://clinicaltrials.gov/)	Accessed in August 2009.	Hepatitis, Alcoholic

CONTRIBUTIONS OF AUTHORS

CG and AR conceived the idea of the review and provided a clinical perspective. KW and AR screened the search results, selected publications for inclusion and exclusion according to the eligibility criteria, extracted data, and made the risk of bias judgements. KW drafted the review and performed the meta-analyses. AR, JW and CG revised the review. JW performed the trial sequential analyses. KW, JW, CG interpreted the data and results. CG provided general advice on the review provided a methodological perspective.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Denmark.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The risk of bias descriptions (funding, early stopping) have been updated in the review, according to The Cochrane Hepato-Biliary group module. In the review 'weighted mean difference' is now called 'mean difference'. We now describe the statistical tests we used for outcome measure data that are reported in only one trial. The secondary outcome measure that was described as 'Liver biochemistry and function' is now described as 'Liver and kidney biochemistry and function'. For the meta-analyses we reported the results from the fixed-effect model, unless there were discrepancies between the statistical significance in the results of the two models, in which case we report both. We removed the proposal to perform 'carry-forward analysis' as a sensitivity analysis, because for the outcome measure mortality it would yield the same result as 'good outcome analysis'. We performed a post-hoc outcome measure on the effect of pentoxifylline on TNF levels.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Hepatitis, Alcoholic [*drug therapy; mortality]; Pentoxifylline [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Tumor Necrosis Factor-alpha [antagonists & inhibitors]

MeSH check words

Humans