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Propylthiouracil for alcoholic liver disease (Review)

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[Intervention Review]

Propylthiouracil for alcoholic liver disease

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ABSTRACT

Background

Randomised clinical trials have addressed the question whether propylthiouracil has any beneficial effects in patients with alcoholic liver disease.

Objectives

To assess the beneficial and harmful effects of propylthiouracil for patients with alcoholic liver disease.

Search methods

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (April 2011), *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (April 2011), *MEDLINE* (1948 to April 2011), *EMBASE* (1980 to April 2011), and *Science Citation Index Expanded* (1900 to April 2011). These electronic searches were combined with full text searches. Manufacturers and researchers in the field were also contacted.

Selection criteria

Randomised clinical trials studying patients with alcoholic steatosis, alcoholic fibrosis, alcoholic hepatitis, and/or alcoholic cirrhosis were included irrespective of blinding, publication status, or language. Interventions encompassed propylthiouracil at any dose versus placebo or no intervention.

Data collection and analysis

All analyses were performed according to the intention-to-treat method in RevMan Analyses. The risk of bias of the randomised clinical trials was evaluated by bias risk domains such as generation of allocation sequence, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, academic bias, and source of funding.

Main results

Combining the results of six randomised clinical trials with high risk of bias which included 710 patients demonstrated no significant effects of propylthiouracil versus placebo on all-cause mortality (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.66 to 1.30), liver-related mortality (RR 0.90, 95% CI 0.58 to 1.40), or complications of the liver disease. Although propylthiouracil was not associated with a significant increased risk of non-serious adverse events, there were occasional instances of serious adverse events such as leukopenia and generalised bullous eruption.

Authors' conclusions

We could not demonstrate any significant beneficial effect of propylthiouracil on all-cause mortality, liver-related mortality, liver complications, or liver histology of patients with alcoholic liver disease. Propylthiouracil was associated with adverse events. Confidence intervals were wide. Thus, the risk of random errors and systematic errors was high. Accordingly, there is no evidence for using propylthiouracil for alcoholic liver disease outside randomised clinical trials.

PLAIN LANGUAGE SUMMARY

Propylthiouracil for alcoholic liver disease

The majority of liver diseases are caused by alcohol in the Western world. Propylthiouracil - an antithyroid drug that is used for patients with raised metabolism - has been suggested as a potential treatment for alcoholic liver disease. Six randomised clinical trials with a total of 710 patients were included in this systematic review. The trials were generally with high risk of bias. We could not demonstrate any significant effect of propylthiouracil on all-cause mortality, liver-related mortality, liver complications, or liver histology of patients with alcoholic liver disease. Although propylthiouracil was not associated with a significant increased risk of non-serious adverse events, there were occasional instances of serious adverse events (leukopenia, generalized bullous eruption). The trials included a small number of patients, and so, the risk of random error (error due to play of chance) is high. There seems to be no evidence for using propylthiouracil for alcoholic liver disease outside randomised clinical trials.

BACKGROUND

Liver fibrosis and liver cirrhosis are common reactions to a number of hepatotoxic substances, hepatotropic viruses, autoimmune liver diseases, metabolic liver diseases, etc. Alcohol and hepatotropic viruses are the cause of the majority of liver fibrosis and cirrhosis in the Western world. For example, the attributable risk for symptomatic liver cirrhosis in Italy explained by alcohol consumption, hepatitis B virus, and hepatitis C virus was 98.1% in men and 67.0% in women (Corrao 1998a).

Alcohol is a major hepatotoxin (Morgan 1999). Alcohol leads to fatty liver (Rubin 1968), alcoholic hepatitis, fibrosis, and cirrhosis (Morgan 1999). Alcoholic hepatitis is associated with peripheral leukocytosis and marked hepatic portal and parenchymal inflammatory infiltration predominantly by neutrophils (Hill 1993; Sheron 1993). Data from long-term studies in which patients with alcoholic fatty change and alcoholic hepatitis were followed for up to 13 years demonstrates that alcoholic hepatitis is a predictor of a later development of liver fibrosis and cirrhosis (Sørensen 1984; Marbet 1987). Alcohol-induced necrosis and inflammation may trigger the scarring and the development of fibrosis, and later on of the development of cirrhosis. In fact, about 70% of patients with clinical alcoholic hepatitis also have alcoholic cirrhosis at the time of diagnosis (Mendenhall 1984). Five-year survival rates in patients with alcoholic cirrhosis who stop drinking are of order of 50% to 75%; whereas survival rates in patients continuing to drink rarely exceed 40% (Powell 1968). The progression of liver fibrosis and cirrhosis in patients with alcohol problems is enhanced by the presence of hepatitis B and hepatitis C virus markers (Chang 1994; Corrao 1998b).

Propylthiouracil (PTU) may reduce alcohol induced hepatocyte damage by acting as an antioxidant (Hicks 1992) and suppressing alcohol induced hepatic necrosis (Israel 1975a). Studies have found a 'hypermetabolic state', with an increase in hepatic oxygen consumption in rats chronically treated with alcohol (Israel 1975a) as well as in alcoholic patients (Iturriaga 1980). PTU, an antithyroid drug (Kampmann 1981; Klein 1994), reacts with some of the oxidizing species derived from the respiratory burst in neutrophils (Imamura 1986; Carmichael 1993; Ross 1998). PTU protects rat liver and isolated hepatocytes from ischaemic damage (Israel 1975b; Younes 1987; Gonzalez-Reimers1988). Therefore, PTU could slow the progression of alcoholic liver disease.

Several randomised clinical trials have addressed the question whether PTU has any efficacy in patients with alcoholic liver disease. The results of these trials have been contradictory (Orrego 1979a; Hallé 1982a; Orrego 1987a). Some investigators found beneficial effects of PTU on all-cause mortality, complications, and biochemistry (Orrego 1979a; Orrego 1987a). Others found no significant effect on all-cause mortality (Hallé 1982a). Based on a questionnaire survey among European hospital-based specialists in gastroenterology/hepatology, 15% of the specialists considered using PTU for alcoholic hepatitis (Gluud 1993). The present systematic review examines the beneficial and harmful effects of PTU for alcoholic liver disease.

OBJECTIVES

To assess the beneficial and harmful effects of PTU versus placebo or no intervention for patients with alcoholic liver disease based on the results of randomised clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised clinical trials were included, irrespective of blinding, publication status, or language. Trials using quasi-randomisation were excluded.

Types of participants

Patients with alcoholic steatosis, alcoholic fibrosis, alcoholic hepatitis, and/or alcoholic cirrhosis were included.

Types of interventions

Peroral or parenteral administration of PTU at any dose versus placebo or no intervention. Additional interventions were allowed, as long as both intervention groups in the individual trial received the additional intervention.

Types of outcome measures

Primary outcomes

1. Number of patients dying (total and liver-related deaths).

Secondary outcomes

1. Development of clinical symptoms and complications (ie, ascites, variceal bleeding, hepatic encephalopathy, hepato-renal syndrome, hepato-cellular carcinoma).
2. Liver biopsy findings.
3. Number and type of adverse events (non-serious and serious). Adverse events were defined as any untoward medical occurrence that did not have a causal relationship with the treatment. Serious adverse events were defined according to the ICH guidelines (ICH-GCP 1997) as any event that would increase all-cause mortality; was life-threatening; required in-patient hospitalisation; resulted in a persistent or significant disability; or any important medical event, which may jeopardise the patient or required intervention to prevent it.
4. Quality-of-life.
5. Health economics.

Search methods for identification of studies

Electronic searches

Relevant randomised clinical trials were identified by searching *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2011), *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE*, and *Science Citation Index Expanded* (Royle 2003). The search strategies applied to the individual electronic databases and the time span of the searches are given in Appendix 1.

Searching other resources

Further trials were identified by reading the reference lists of the identified studies.

The principal authors of the identified randomised clinical trials were approached and inquired about additional randomised clinical trials they might know. Pharmaceutical companies involved in the production of PTU were contacted in order to obtain unpublished randomised clinical trials.

Data collection and analysis

The meta-analyses were conducted according to the published protocol (Rambaldi 2001a) as recommended by The Cochrane Collaboration (Higgins 2011) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2011).

Patient characteristics, diagnosis, and treatments

The following data were recorded from the individual randomised clinical trials: mean (or median) age, sex ratio, alcohol consumption, form of liver disease, etiology of liver disease, duration of liver disease, severity of liver disease at entry, type and dose of PTU intervention, and type of intervention in the control group. The diagnostic work-up before entry was registered, specifically if hepatitis markers were evaluated and the types of alcoholic liver disease excluded were specified. Development of clinical symptoms and complications, liver biochemistry, liver function, liver biopsy findings, alcohol consumption, quality-of-life, health economics (ie, length of hospital stay, cost of medication, and cost of additional follow-up weighted against any gains in health), and adverse events during follow-up were registered.

Selection and data-extraction bias

All randomised clinical trials considered for inclusion were analysed by the contributors, who planned to confer with an 'ombudsman' in case disagreements could not be solved. Such cases did not occur.

All randomised clinical trials had the pertinent data extracted by the contributors.

All identified trials were listed and trials excluded from the meta-analysis of the review were identified with the reason for exclusion.

Assessment of risk of bias

The risk of bias in the randomised clinical trials was assessed using generation of allocation sequence, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, baseline imbalance, early stopping, academic bias, source of funding (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Gurusamy 2009; Gluud 2011; Higgins 2011). Quality components were classified as follows:

Sequence generation

- Low risk of bias (the methods used are either adequate (eg, computer generated random numbers, table of random numbers) or unlikely to introduce confounding).
- Uncertain risk of bias (there is insufficient information to assess whether the method used is likely to introduce confounding).
- High risk of bias (the method used (eg, quasi-randomised studies) is improper and likely to introduce confounding).

Allocation concealment

- Low risk of bias (the method used (eg, central allocation) is unlikely to induce bias on the final observed effect).
- Uncertain risk of bias (there is insufficient information to assess whether the method used is likely to induce bias on the estimate of effect).
- High risk of bias (the method used (eg, open random allocation schedule) is likely to induce bias on the final observed effect).

Blinding of participants, personnel, and outcome assessors

- Low risk of bias (blinding was performed adequately, or the outcome measurement is not likely to be influenced by lack of blinding).
- Uncertain risk of bias (there is insufficient information to assess whether the type of blinding used is likely to induce bias on the estimate of effect).
- High risk of bias (no blinding or incomplete blinding, and the outcome or the outcome measurement is likely to be influenced by lack of blinding).

Incomplete outcome data

- Low risk of bias (the underlying reasons for missingness are unlikely to make treatment effects departure from plausible values, or proper methods have been employed to handle missing data).
- Uncertain risk of bias (there is insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias on the estimate of effect).
- High risk of bias (the crude estimate of effects (eg, complete case estimate) will clearly be biased due to the underlying reasons for missingness, and the methods used to handle missing data are unsatisfactory).

Selective outcome reporting

- Low risk of bias (the trial protocol is available and all of the trial's pre-specified outcomes that are of interest in the review have been reported or similar; if the trial protocol is not available, all the primary outcomes in this review are reported).
- Uncertain risk of bias (there is insufficient information to assess whether the magnitude and direction of the observed effect is related to selective outcome reporting).
- High risk of bias (not all of the trial's pre-specified primary outcomes have been reported or similar).

Other bias

Academic bias

- Low risk of bias (the author of the trial has not conducted previous trials addressing the same interventions).
- Uncertain risk of bias (It is not clear if the author has conducted previous trials addressing the same interventions).
- High risk of bias (the author of the trial has conducted previous trials addressing the same interventions).

Source of funding bias

- Low risk of bias (the trial's source(s) of funding did not come from any parties that might have conflicting interest (eg, drug manufacturer).
- Uncertain risk of bias (the source of funding was not clear).
- High risk of bias (the trial was funded by a drug manufacturer).

We classified trials as trials with low risk of bias if they were judged with low risk of bias in all the above domains. Otherwise, the trials were classified as trials with high risk of bias.

Statistical methods

All analyses were performed according to the intention-to-treat method including all randomised patients. Patients without the outcome variable were included in two analyses; one in which patients without the outcome were considered as failures, and one in which patients without the outcome were considered as successes.

The statistical package Review Manager provided by The Cochrane Collaboration was used (RevMan 2011). For all analyses we used both random-effects (DerSimonian 1986) and fixed-effect (DeMets 1987) models. In case of discrepancy between the two models (one showing a significant intervention effect and the other no significant intervention effect) we reported both results. Otherwise, we reported only the results from the fixed-effect model. Discrepancy only occurred when there was heterogeneity (please see below). In case of discrepancy between the two models, we put most weight on the results of the fixed-effect model if the meta-analysis included one or more large trials with adequate methodology. Large trials were defined as trials that included more than half of all included events and participants in the meta-analysis. Otherwise, we put most weight on the random-effects model. The reason for this is that the random-effects model puts more weight on small trials. Small trials are more often than large trials conducted with unclear or inadequate methods (Kjaergard 2001).

Dichotomous data were analysed by calculating the relative risks (RR) and continuous outcomes as mean difference (MD) both with 95% confidence intervals.

We conducted trial sequential analysis in order to estimate how far we had come in our development of the cumulative evidence (Wetterslev 2008; Thorlund 2009; Brok 2009). We based our trial sequential analysis on all-cause mortality using an outcome proportion of 15% in the control group; an assumed relative risk reduction of 20%; an alpha of 5%; a beta of 20%; and a heterogeneity correction for the calculation of the required information size (Wetterslev 2008).

Heterogeneity and funnel plot asymmetry

Heterogeneity in the results of the trials was initially assessed by the inspection of graphical presentations and by calculating a test of heterogeneity (Chi-square) as well as level of inconsistency (I^2). We anticipated between-trial variation in estimation of morbidity and all-cause mortality for those patients who presented with advanced liver disease (DerSimonian 1986; DeMets 1987). Subgroup analyses were performed in order to assess the impact of these possible sources of heterogeneity on the main results.

Potential causes for heterogeneity were explored by performing sensitivity analyses. We performed sensitivity analyses with regard to methodological quality of included randomised clinical trials (analysing separately randomised clinical trials with adequate quality components, ie, low risk of bias, and inadequate quality components, high risk of bias, and duration of treatment. We also planned analyses regarding way of administration of PTU as well as preparation and dose of PTU, but all trials used per oral PTU 300 mg per day.

Due to the risk of chance statistical findings, such findings were interpreted conservatively.

Potential publication bias (Vickers 1998) and other sources of bias were planned to be investigated by funnel plots (Egger 1997), but due to the few randomised clinical trials identified, we did not perform such analyses.

RESULTS

Description of studies

Searches

Electronic searches (through April 2011) of *The Cochrane Hepato-Biliary Group Controlled Trials Register* (n = 17 publications), *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (n = 19 publications), *MEDLINE* (n = 16 publications), *EMBASE* (n = 48 publications), and *Science Citation Index Expanded* (n = 13 publications) identified a total of 113 publications. Out of these publications, three randomised clinical trials described in ten publications were identified (Orrego 1979; Hallé 1982; Orrego 1987). By reading bibliographies we identified four further abstracts on three randomised clinical trials (Serrano-Cancino 1981; Pierrugues 1989; Rodriguez 1993), which were not identified by the electronic searches.

Included studies

The individual randomised clinical trials are described in the table of 'Characteristics of included randomised clinical trials'. In total, six randomised clinical trials reported the random allocation of patients with alcoholic liver disease (n = 710) to PTU versus placebo in 14 publications. No randomised clinical trials comparing PTU versus no intervention were identified.

The entry criteria in the randomised clinical trials varied, but the inclusion criteria were generally of good quality making it highly likely that all patients did in fact have alcoholic liver disease.

The dosage of PTU was 300 mg orally per day in all the trials. The duration of the treatment was within 46 days in five of the trials (Orrego 1979; Serrano-Cancino 1981; Hallé 1982; Pierrugues 1989; Rodriguez 1993), and the treatment duration was 24 months in the remaining trial (Orrego 1987) .

Excluded studies

A total of two studies with reasons of exclusion are listed under 'Characteristics of excluded studies'.

Risk of bias in included studies

The method to generate the allocation sequence was considered adequate in three randomised clinical trials (Orrego 1979; Orrego 1987; Rodriguez 1993).

The method to conceal the allocation sequence was considered adequate in two randomised clinical trials (Orrego 1979; Rodriguez 1993).

All randomised clinical trials were described as 'double blind'. In four randomised clinical trials (Orrego 1979; Hallé 1982; Orrego 1987; Rodriguez 1993) placebo was described as having an identical presentation, making it likely that both investigators and patients were blinded.

Four randomised clinical trials were considered free of incomplete outcome data (Orrego 1979; Hallé 1982; Orrego 1987; Rodriguez

1993), and in the other two (Serrano-Cancino 1981; Pierrugues 1989) there was not sufficient information regarding this item.

All randomised clinical trials were considered free of selective reporting, and academic bias.

None of the authors declared the source of funding of the included trials.

Effects of interventions

All-cause mortality

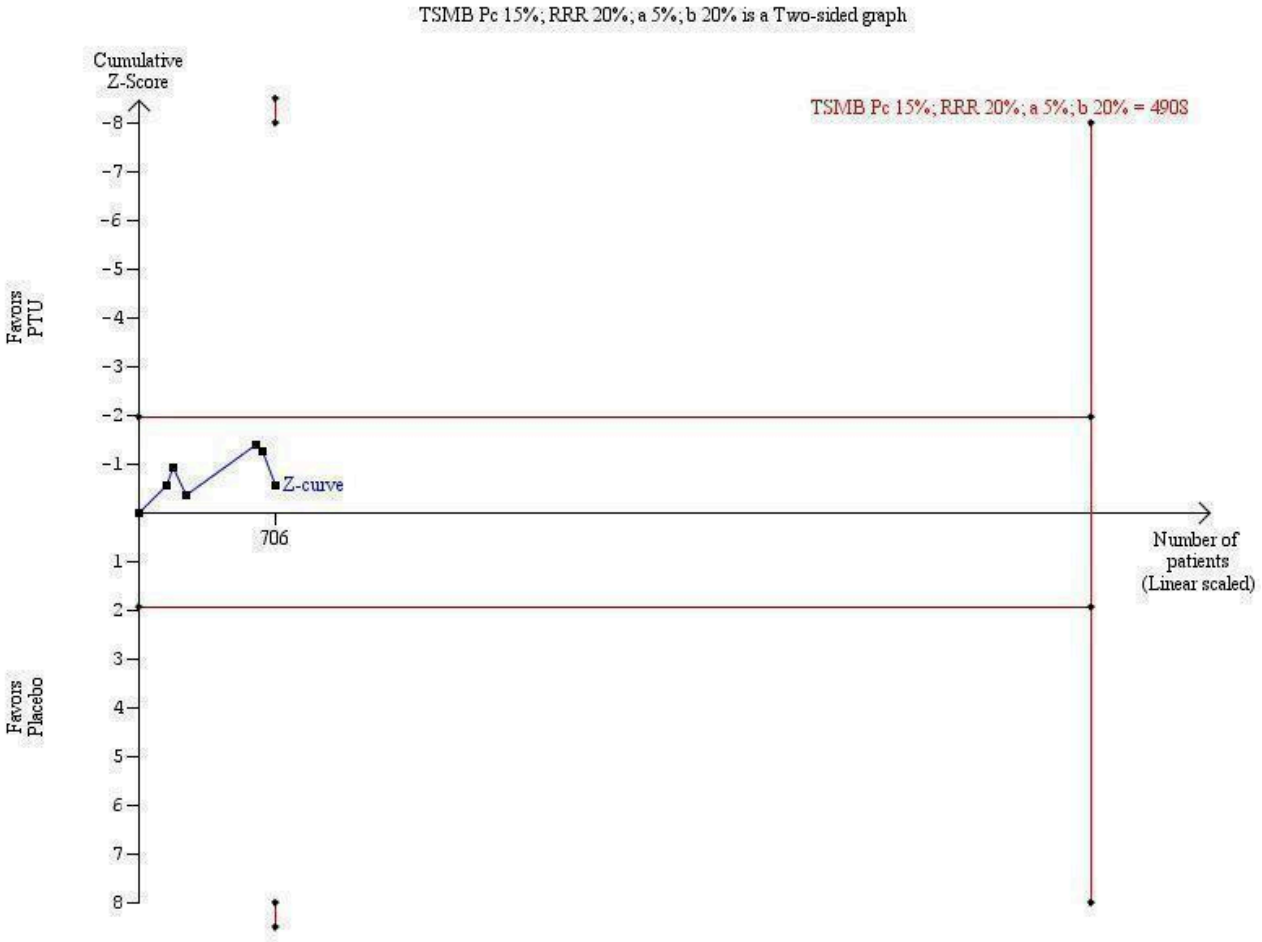
Combining the results of the six randomised clinical trials demonstrated no significant effect of PTU versus placebo on all-cause mortality (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.66 to 1.30). In the PTU group, 50/353 (14.2%) patients died versus 54/357 (15.1%) patients in the placebo group (Analysis 1.1).

Sensitivity analysis stratifying the randomised clinical trials according to the risk of bias in the trials (trials at low risk of bias versus high risk of bias for each domain, excluding the report 'free of source of funding' which was unclear in all trials) did not demonstrate differences regarding the intervention efficacy of PTU on all-cause mortality between randomised clinical trials at low risk versus high risk of bias (Analysis 3.1).

Sensitivity analysis stratifying the randomised clinical trials according to the duration of treatment did not change this estimate significantly. The RR of death of the randomised trials with a short-term treatment (within 46 days) was 1.19 (95% CI 0.78 to 1.81) and the RR of the randomised trial with a treatment duration of 24 months was 0.63 (95% CI 0.35 to 1.13) (Analysis 3.2). Stratifying the randomised clinical trials according to a worst-best case scenario analysis (all patients who dropped-out or were withdrawn were considered dead), or a per-protocol analysis did not change this estimate significantly (Analysis 3.3; Analysis 3.4).

Trial sequential analysis based on a heterogeneity-corrected information size of 4908 patients shows that with only 706 patients randomised, we are still very early in the development of evidence regarding this intervention (Figure 1).

Figure 1. Trial sequential analysis of all-course mortality of patients with alcoholic liver disease included in randomised clinical trials on propylthiouracil versus placebo. The heterogeneity-corrected required information size of 4908 patients is based on an event proportion of 15% in the control group (Pc); a relative risk reduction (RRR) of 20% (to an event proportion of 13%) in the experimental group; an alpha of 5%; a beta of 20%; and a heterogeneity of 17%.



Liver-related mortality
Combining the results of four randomised clinical trials, which provided data on liver mortality, showed no significant effect of PTU versus placebo on this outcome (RR 0.90, 95% CI 0.58 to 1.40) (Orrego 1979; Hallé 1982; Orrego 1987; Rodriguez 1993). In the PTU group, 33/316 (10.4%) patients died a liver-related death versus 37/320 (11.6%) patients in the placebo group (Analysis 1.2).

Liver complications
No significant effect of PTU versus placebo could be demonstrated on hepatic encephalopathy (RR 0.84, 95% CI 0.39 to 1.83) (Hallé 1982) (Analysis 1.3).

No significant effect of PTU versus placebo could be demonstrated on ascites (RR 2.32, 95% CI 0.22 to 24.40) (Hallé 1982) (Analysis 1.4).

No significant effect of PTU versus placebo could be demonstrated on variceal bleeding (RR 1.48, 95% CI 0.63 to 3.47) (Hallé 1982) (Analysis 1.5).

No significant effect of PTU versus placebo could be demonstrated on hepato-renal syndrome (RR 0.84, 95% CI 0.39 to 1.83) (Hallé 1982) (Analysis 1.6).

Liver histology
Due to the paucity of data on liver histology we did not assess this outcome. Only one trial reported as an abstract, provided data on histological changes (which were similar in PTU and placebo group) (Pierrugues 1989). In three trials, a liver biopsy was done at the beginning of the trial or at some time after in a subgroup of patients, but no data on liver histology at the end of the follow-up were reported (Orrego 1979; Hallé 1982; Orrego 1987).

Adverse events
Combining the results of the five randomised clinical trials demonstrated no significant effect of PTU on serious adverse events (RR 1.67, 95% CI 0.28 to 10.03). In the PTU group 2/100 (2%) patients had serious adverse events (marked leukopenia, generalized bullous eruption) versus 1/110 (0.9%) patients in the placebo group (leukopenia) (Analysis 2.1).

Combining the results of the same five randomised clinical trials demonstrated no significant effects of PTU on non-serious adverse events (RR 1.41, 95% CI 0.40 to 5.01). In the PTU group 5/100 (5%) patients had non-serious adverse events versus 4/110 (3.6%) patients in the placebo group (Analysis 2.2). The adverse events included rash and hypothyroidism.

In one trial, 24 adverse events were reported (15 rashes, 8 leukopenia, thrombocytopenia); 15 adverse events occurred in the PTU group and 9 in the placebo group (the differences between groups were not statistically significant), but the number of serious and non-serious adverse events in each group was not specified (Orrego 1987).

Quality-of-life and health economics
None of the randomised clinical trials examined quality-of-life or health economics.

Funnel plot asymmetry
Due to the paucity of randomised clinical trials and observed outcome measures reported in the included trials, we did not try to analyse for funnel plot asymmetry.

DISCUSSION

We could not demonstrate any significant effects of PTU on all-cause mortality, liver-related mortality, and liver complications when tested against placebo in patients with alcoholic liver disease. However, absence of evidence is not evidence of absence of effect.

The lack of effect of PTU on all-cause mortality was robust to sensitivity analyses taking the risk of bias in the randomised clinical trials into consideration. The sensitivity analyses contrasting trials of low risk of bias versus trials of high risk of bias as judged by the single domain did not reveal any significant influence on the RR of all-cause mortality. This is in contrast to studies examining the association between intervention effects and risk of bias of randomised clinical trials (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008). However, one should notice that two randomised clinical trials at high risk of bias were only reported as abstracts. First, the brevity of abstracts may make it difficult to report the risk of bias in a trial in sufficient detail. Second, the association between the risk of bias and intervention effects previously reported rests mainly or exclusively on trials reported as full articles (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008).

Sensitivity analysis taking duration of treatment into consideration showed no significant difference on the RR of all-cause mortality. The worst-best case scenario analysis and the per-protocol analysis did not show any significant effect of PTU on all-cause mortality.

Our trial sequential analysis demonstrates that we are very early in our development of evidence on PTU for all-cause mortality in alcoholic liver disease with only 706 patients randomised. We are still far from obtaining conclusive evidence on the effect of PTU for patients (Figure 1).

We were unable to detect any significant influence of PTU on liver histology due to the paucity of data. Only one trial (Pierrugues 1989), reported as an abstract, provided data on histological changes (which were similar in PTU and placebo group). In three studies (Orrego 1979; Hallé 1982; Orrego 1987), a liver biopsy was done at the beginning of the trial or at some time after in a subgroup of patients, but no data on liver histology at the end of the follow-up were reported.

Although propylthiouracil was not associated with a significant increased risk of non-serious adverse events, there were occasional instances of serious adverse events: one patient with leukopenia and one patient with generalised bullous eruption, and the latter patient died during the randomised clinical trial. Few patients with PTU induced fulminant hepatitis and a number of adverse events have been reported in the literature during PTU treatment for hyperthyroidism (Deidiker 1996; Ichiki 1998), eg, transient asymptomatic PTU hepatotoxicity occurs in one-third of patients (Huang 1994) together with acute cases of interstitial nephritis, vasculitis, Stevens-Johnson syndrome, and other adverse events (Dysseleer 2000; Morita 2000). Indeed, hypothyroidism was a non-serious adverse event in some patients, and it could have been the reason of some dropouts in the trials (Hallé 1982).

The rationale behind PTU for alcoholic liver disease has been said to be via an effect on hepatic oxygen consumption (eg, Yuki 1982; Carmichael 1993). Contrary to observations in normal rats (Kawasaki 1989), however, PTU 300 mg or 600 mg intravenously were without significant effects on arterial and venous oxygen

content in patients with alcoholic cirrhosis with or without alcoholic hepatitis (Sogni 1997). Furthermore, the latter study was unable to demonstrate any effects of PTU on systemic and splanchnic haemodynamics of these patients (Sogni 1997). These findings are contradictory to some extent to the Rojeter et al study (Rojter 1995), which examined haemodynamics measured by the Doppler technique. According to the latter study, PTU administration caused a significant increase in portal blood flow in patients with alcoholic cirrhosis.

We could not demonstrate any significant effect of PTU on any clinically important outcomes of patients with alcoholic liver disease. Accordingly, there seems to be no evidence for using PTU for alcoholic liver disease. The absence of evidence for an effect of PTU on clinically relevant outcome variables, however, does not exclude the possibility that PTU may possess effects. Ioannidis and Lau recently applied 'recursive cumulative meta-analyses' of randomised clinical trials to evaluate the relative change in the pooled treatment effect over time for 60 medical interventions within pregnancy/perinatal medicine and cardiology (Ioannidis 2000). With 500 accumulated patients, the pooled relative risk may change by about 0.6 to 1.7 fold in the immediate future. When 2000 patients have been randomised, the pooled relative risk may change by 0.7 to 1.3 fold. With only 710 patients with alcoholic liver disease randomised to PTU versus placebo and the wide confidence intervals of the estimates we cannot rule out a potential efficacy of PTU for alcoholic liver disease. However, if clinicians wish to treat patients with alcoholic liver disease with PTU, they must first conduct new randomised clinical trials. Such randomised clinical trials ought to be large, conducted with adequate methodology, the treatment period ought to be several years, and efficacy and harmful effects ought to be closely monitored by an independent data monitoring and safety committee.

A number of medical interventions has been used for alcoholic liver disease (Gluud 1993), including colchicine (Rambaldi 2005a), glucocorticosteroids (Christensen 1995; Gluud 2001), anabolic-androgenic steroids (Gluud 1988; Rambaldi 2006a), insulin/glucagon (Trinchet 1992), milk thistle (Flora 1998, Rambaldi 2007), parenteral amino acid supplementation (Mezey 1991), S-adenosyl-L-methionine (Mato 1999), and polyenylphosphatidylcholine (Lieber 2000; Lieber 2003). None of these interventions have been demonstrated effective in systematic reviews of randomised clinical trials. S-adenosyl-L-methionine may be a promising intervention for alcoholic liver disease (Mato 1999), but more randomised clinical trials are needed before this treatment can be recommended (Rambaldi 2006b). Pentoxiphylline has only been assessed in one small trial (Akriviadis 2000), and liver transplantation has never been assessed in randomised trials. Based on a matched and simulated control study, liver transplantation seems to work for patients with Child-Pugh C class cirrhosis, but not significantly so for Child-Pugh A and B class cirrhosis (Poynard 1994; Poynard 1999). The results of more randomised clinical trials must be awaited before we may have an efficient medical intervention for alcoholic liver disease.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review could not demonstrate any significant beneficial effect of PTU on any clinically meaningful outcomes (all-cause mortality, liver-related mortality, and liver complications) of patients with alcoholic liver disease. PTU is associated with serious adverse events. Accordingly, there is no indication for using PTU for alcoholic liver disease outside randomised clinical trials.

Implications for research

The absence of evidence for an effect of PTU on clinically relevant outcome variables, however, does not exclude the possibility of an effect. If researchers wish to conduct new randomised clinical trials they ought to be large, conducted with adequate methodology, the treatment period ought to be several years, and efficacy and harmful effects ought to be closely monitored by an independent data monitoring and safety committee. Such trials ought to follow the Consolidated Standards for Reporting Trials (CONSORT) Statement (www.consort-statement.org).

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Peer Reviewers: Alastair Burt, UK; Saboor A Khan, UK.
Contact Editor: Robert Sutton, UK.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hallé 1982

Methods	Randomised clinical trial.
Participants	Sixty-seven patients with severe alcoholic hepatitis. Thirty-one patients (29 males and two females, mean age 40 ± 2 years (y)) received PTU, while 36 patients (32 males and four females, mean age 38.9 ± 1 y) received placebo. Inclusion criteria: heavy ethanol ingestion and clinical diagnosis of ALD. All had serum bilirubin > 5 mg/dl and at least one of the following: hepatic tenderness, fever above 100 degrees Fahrenheit, or leukocytosis above 12,000 per mm^3. Exclusion criteria: serious bacterial infection, massive gastrointestinal bleeding, preexisting renal failure, and previous or current thyroid disease.
Interventions	Experimental group: PTU 75 mg orally every six hours. Control group: placebo. Duration of the treatment: six weeks. Duration of follow-up: eight weeks.
Outcomes	All-cause mortality. Complications. Biochemistry. Liver histology. Adverse events.
Notes	Sent letter in 2001. Dr. Reynolds answered, but no additional data were obtained. Seventy-one patients were randomised, but two patients refused participation and two patients were withdrawn as s-bilirubin was < 5 mg/dl at randomisation.
Risk of bias	

Hallé 1982 *(Continued)*

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: double blind with placebo of identical presentation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The post-randomisation drop-outs unlikely to result in a change in the effect estimate.
Selective reporting (reporting bias)	Low risk	All the important outcomes were reported.
Free of academic bias	Low risk	Comment: No previous trial of the same comparison by the same authors was identified.

Orrego 1979

Methods	Randomised clinical trial.
Participants	A total of 143 patients (69 in the PTU and 74 in placebo group) were included in the trial. Inclusion criteria: excessive drinking, and well-documented history of spree-drinking. The criteria for diagnosing liver disease required one or more of the following clinical findings: hepatomegaly, tender liver, jaundice, ascites, collateral circulation, spider nevi, and splenomegaly. Further, at least two of the following abnormal laboratory tests were required: s-aspartate aminotransferase, s-alanine aminotransferase, s-gamma glutamyltranspeptidase, s-alkaline phosphatase, s-total bilirubin. In 79 patients in whom the prothrombin time permitted, liver biopsies were performed at 7.6 ± 0.1 day after admission. All biopsy specimens were classified in: fatty liver, alcoholic hepatitis, and cirrhosis without hepatitis. The three histologically diagnosed groups were analysed separately. Exclusion criteria: hypothyroidism; diabetes; other therapies that contraindicated the use of PTU; congestive heart failure. The indications for being withdrawn from the study were massive gastrointestinal bleeding, incapacity to ingest drug, leukopenia, or adverse reactions.
Interventions	Experimental group: PTU 300 mg orally every day. Control group: placebo. Maximum period of treatment and of follow-up: 46 days. Patients could be discharged before this period if clinical improvement made further stay in the hospital unnecessary.
Outcomes	All-cause mortality. Biochemistry. Liver histology. Adverse events. Thyroid function. A Composite Clinical and Laboratory Index was developed for assessing efficacy. The scoring system was based on the concept that the severity of the disease was proportional to the number of abnormal clinical and laboratory findings. The index included signs and symptoms (hepatomegaly, splenomegaly, ascites, encephalopathy, bleeding tendency, spider naevi, palmar erythema, collateral circulation, peripheral edema, anorexia, and weakness) and laboratory tests (s-bilirubin, prothrombin time, s-albumin, s-gamma glutamyltranspeptidase, s-glutamic oxalacetic transaminase) and depending on the finding, a score (0 to 27) was added for each patient.

Orrego 1979 *(Continued)*

	See also Orrego et al (Orrego 1987b).
Notes	Sent letter in 2001. No reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: generation of allocation sequence by computer.
Allocation concealment (selection bias)	Low risk	Comment: allocation concealment involved an independent pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: double blind with placebo of identical presentation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The post-randomisation drop-outs unlikely to result in a change in the effect estimate.
Selective reporting (reporting bias)	Low risk	All the important outcomes were reported.
Free of academic bias	Low risk	Comment: No previous trial of the same comparison by the same authors was identified.

Orrego 1987

Methods	Randomised clinical trial.
Participants	A total of 360 patients were included in the study, 182 in PTU group (152 males and 30 females, mean age (standard error of the mean (SEM)) 49.2 ± 0.8 y and 178 in the placebo group (139 males and 39 females), mean age (SEM) 49.6 ± 0.8 y. Inclusion criteria: a) alcoholism, defined as excessive drinking or spree drinking consisting of repeated prolonged inebriations or a well documented history of > 80 g of ethanol per day; and b) a clinical and laboratory evidence of liver disease. The severity of disease in each patient were determined with use of the clinical and laboratory index. Exclusion criteria: hepatoma, presence of the hepatitis B surface antigen, contraindications to PTU therapy, and a history of hypothyroidism.
Interventions	Experimental group: PTU 150 mg every 12 h orally every day. Because of the risk of severe hypothyroidism, patients in the PTU group were automatically switched every three months by the pharmacy to the placebo for one month, after which they were again given PTU. Control group: placebo. Additional treatment: 15 mg of riboflavin, a fluorescent compound that was used as a marker of compliance. Most of the urine samples contained the riboflavin marker (93.2 ± 0.8 percent in the placebo group, while 93.1 ± 0.7 percent in the PTU group). Maximum period of treatment: 24 months.

Orrego 1987 *(Continued)*

Outcomes	All-cause mortality. Biochemistry. Liver histology. Adverse events. Alcohol consumption. Thyroid function. This trial also evaluated efficacy with the Combined Clinical and Laboratory Index similar to that of Orrego 1979, but not identical to it (score range 0 to 25).
Notes	Sent letter in 2001. No reply. Only 310 compliant patients form the basis of the reports of the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: generation of allocation sequence by computer.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: double blind with placebo of identical presentation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The post-randomisation drop-outs unlikely to result in a change in the effect estimate.
Selective reporting (reporting bias)	Low risk	All the important outcomes were reported.
Free of academic bias	Low risk	Comment: No previous trial of the same comparison by the same authors was identified.

Pierrugues 1989

Methods	Randomised clinical trial.
Participants	Twenty-nine patients were included in the study (17 males and 12 females, mean age 45.8 years ± 11) with alcoholic hepatitis, 14 in the PTU group and 15 in the placebo group. Diagnostic assessment: alcoholic hepatitis with liver biopsy.
Interventions	Experimental group: PTU 300 mg/day orally. Control group: placebo. Duration of treatment: 28 days.
Outcomes	All-cause mortality. Biochemistry. Liver histology. Thyroid function.

Pierrugues 1989 *(Continued)*

Notes	Sent letter in 2001. No reply. Only published as abstract. A composite clinical and laboratory index was used to evaluate the effect of PTU, but details on which index that was used are not given.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	Low risk	All the important outcomes were reported.
Free of academic bias	Low risk	Comment: No previous trial of the same comparison by the same authors was identified.

Rodriguez 1993

Methods	Randomised clinical trial.
Participants	The trial was stopped when 66 patients with acute alcoholic hepatitis were included, 34 in PTU and 32 in placebo group, because a trend was observed to higher all-cause mortality rates in the PTU group (35.3% in the PTU versus 18.8% in the placebo group), despite nearly identical Maddrey's discriminant function (51.78 ± 34.9 in PTU group versus 53.72± 34.9 in the placebo group) and Child Pugh's score (11.06 ± 1.98 in the PTU group versus 10.72± 1.91 in the placebo group) at entry. Inclusion criteria: patients were all heavy drinkers presenting with s-bilirubin > 4 mg/dl and fever or hepatic tenderness or more than 12000 leukocytes/mm3 in the absence of acute infection.
Interventions	Experimental group: PTU 300 mg/day orally. Control group: placebo. Duration of treatment: 40 days.
Outcomes	All-cause mortality. Complications Biochemistry. Liver histology. Adverse events. Thyroid function.
Notes	Sent letter in 2001. Dr. Gonzalez-Reimers answered, providing additional data. Only published as abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: generation of allocation sequence by computer.

Rodriguez 1993 *(Continued)*

Allocation concealment (selection bias)	Low risk	Comment: allocation concealment involved an independent observer.
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: double blind with placebo of identical presentation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The post-randomisation drop-outs unlikely to result in a change in the effect estimate.
Selective reporting (reporting bias)	Low risk	All the important outcomes were reported.
Free of academic bias	Low risk	Comment: No previous trial of the same comparison by the same authors was identified.

Serrano-Cancino 1981

Methods	Randomised clinical trial.
Participants	Forty-one patients were studied with severe alcoholic hepatitis (21 in the PTU and 20 in the placebo group). At entry there were no significant difference in the clinical severity (ascites, encephalopathy, s-bilirubin, s-albumin, s-creatinin, white blood cell count) between the placebo and the PTU group.
Interventions	Experimental group: PTU 100 mg every eight hours orally. Control group: placebo. Duration of treatment: 17.0 ± 13.3 days. Additional treatment in both groups: standard nutritional and supportive diet.
Outcomes	All-cause mortality. Biochemistry. Adverse events. Duration of hospital stay.
Notes	Sent letter in 2001. No reply. Only published as abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	Low risk	All the important outcomes were reported.
Free of academic bias	Low risk	Comment: No previous trial of the same comparison by the same authors was identified.

PTU = propylthiouracil.

y = year(s).
h = hour(s).
> = more than, greater than.
< = less than.

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

Study	Reason for exclusion
Rojter 1995	The study is observational (case series). In eight patients with alcoholic liver cirrhosis mean arterial pressure and portal blood flow were measured before and after placebo and PTU administration. PTU administration caused a significant increase in portal blood flow in patients with alcoholic cirrhosis.
Sogni 1997	The study is observational (case series). Systemic haemodynamics and splanchnic haemodynamics were not modified after the administration of PTU to 12 patients with alcoholic cirrhosis.

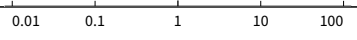
DATA AND ANALYSES

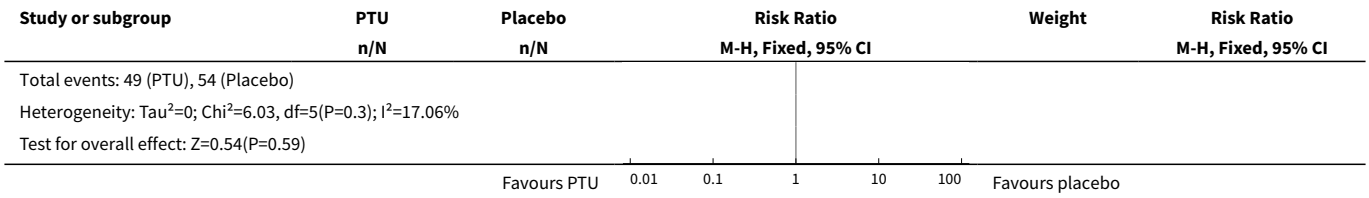
Comparison 1. Propylthiouracil (PTU) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	706	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.28]
2 Liver-related mortality	4	636	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.40]
3 Hepatic encephalopathy	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.39, 1.83]
4 Ascites	1	67	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [0.22, 24.40]
5 Variceal bleeding	2	133	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.63, 3.47]
6 Hepato-renal syndrome	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.39, 1.83]

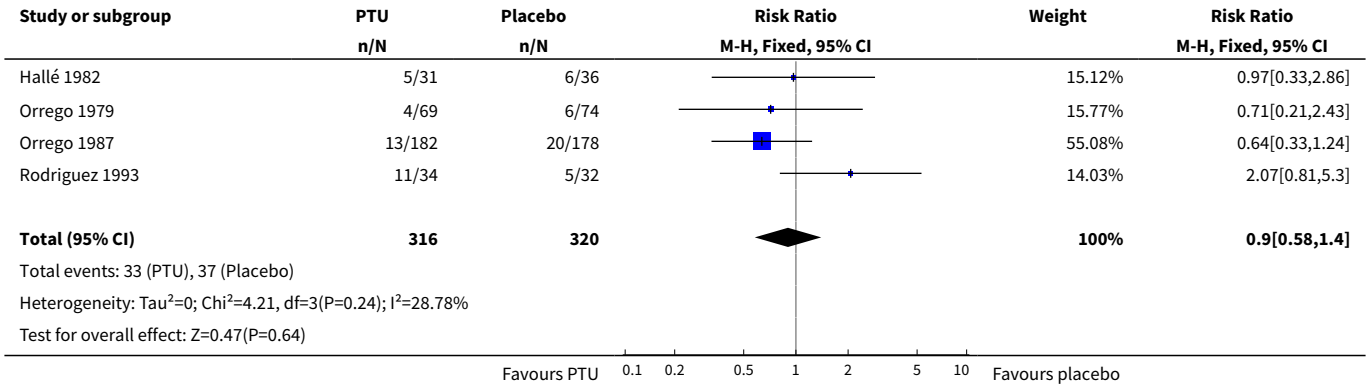
Analysis 1.1. Comparison 1 Propylthiouracil (PTU) versus placebo, Outcome 1 Mortality.

Study or subgroup	PTU n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hallé 1982	8/31	7/36		11.9%	1.33[0.54,3.24]
Orrego 1979	4/69	6/74		10.63%	0.71[0.21,2.43]
Orrego 1987	16/182	25/178		46.42%	0.63[0.35,1.13]
Pierrugues 1989	1/14	0/15		0.89%	3.2[0.14,72.62]
Rodriguez 1993	12/34	6/32		11.35%	1.88[0.8,4.42]
Serrano-Cancino 1981	8/21	10/20		18.81%	0.76[0.38,1.53]
Total (95% CI)	**351**	**355**		**100%**	**0.91[0.65,1.28]**

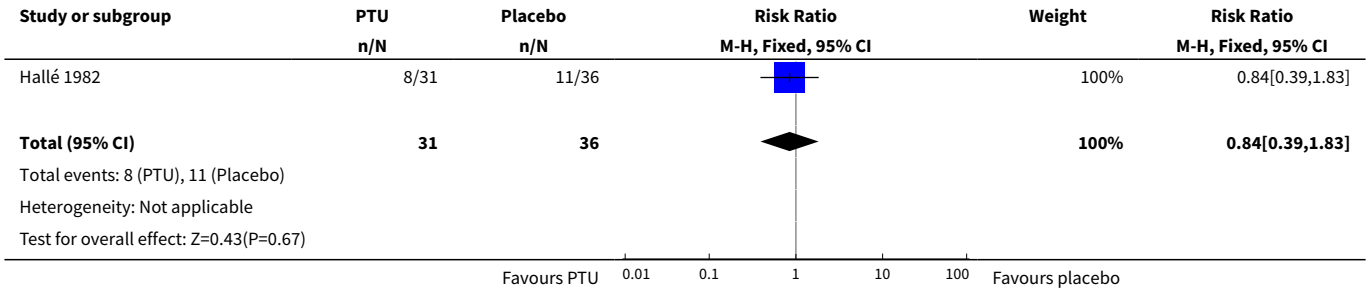




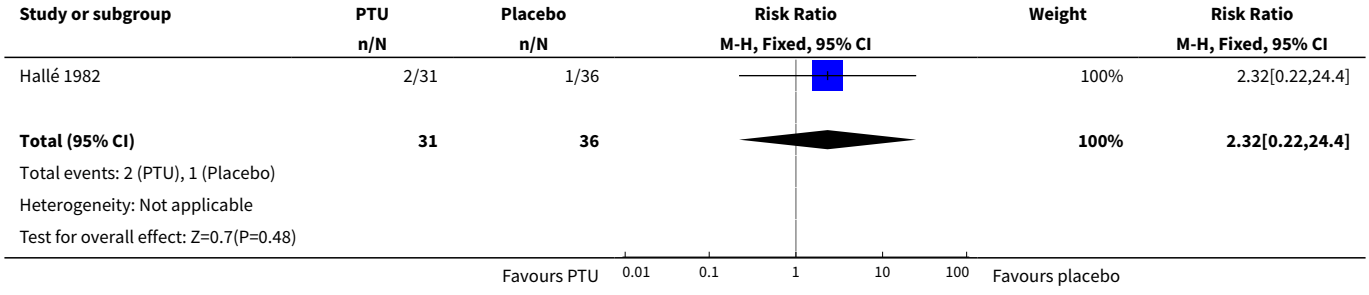
Analysis 1.2. Comparison 1 Propylthiouracil (PTU) versus placebo, Outcome 2 Liver-related mortality.



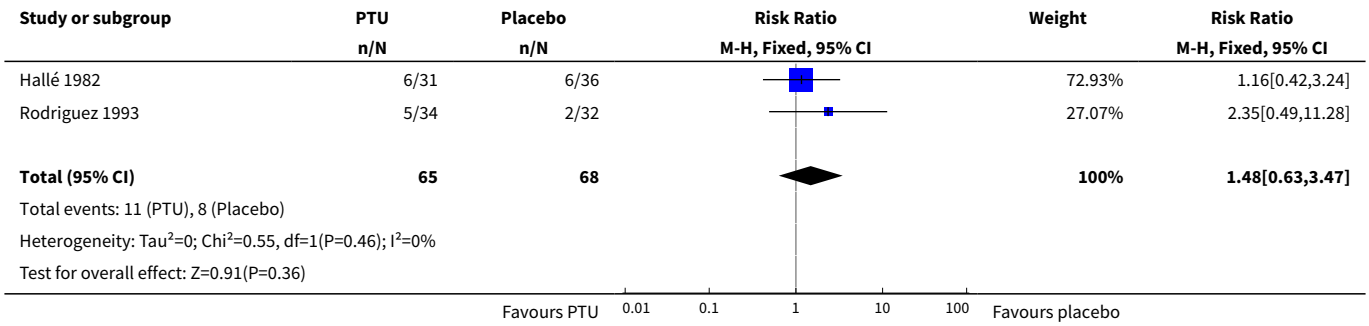
Analysis 1.3. Comparison 1 Propylthiouracil (PTU) versus placebo, Outcome 3 Hepatic encephalopathy.



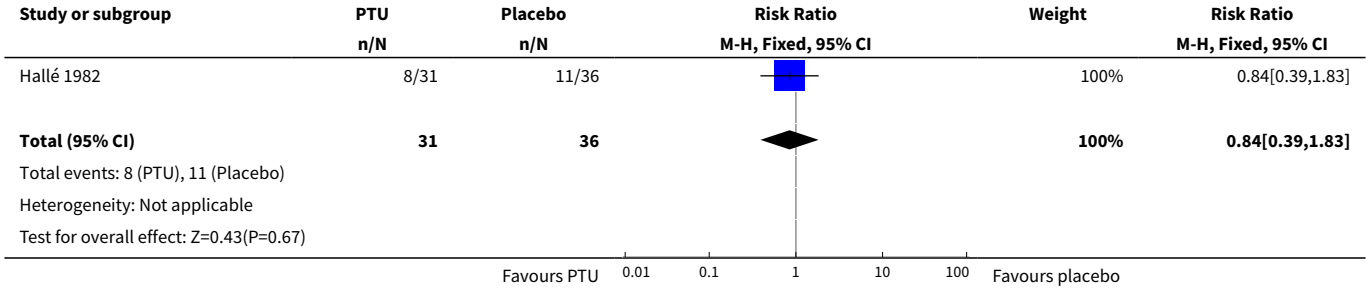
Analysis 1.4. Comparison 1 Propylthiouracil (PTU) versus placebo, Outcome 4 Ascites.



Analysis 1.5. Comparison 1 Propylthiouracil (PTU) versus placebo, Outcome 5 Variceal bleeding.



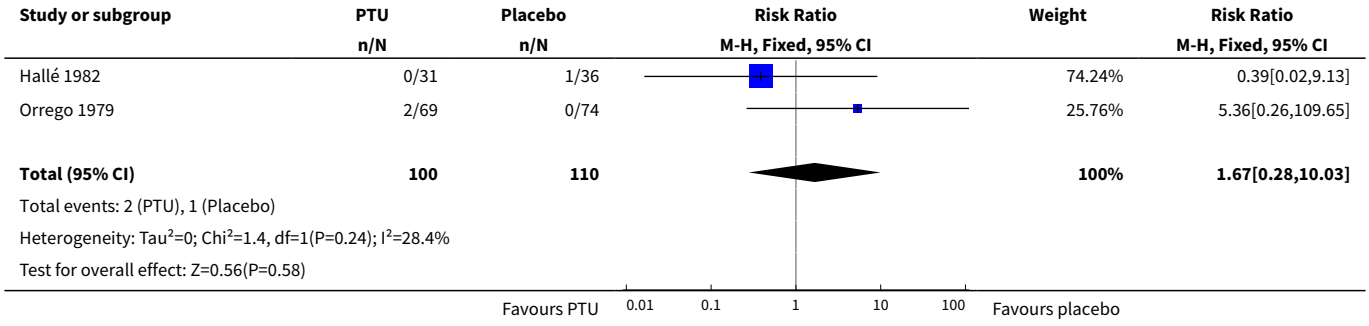
Analysis 1.6. Comparison 1 Propylthiouracil (PTU) versus placebo, Outcome 6 Hepato-renal syndrome.



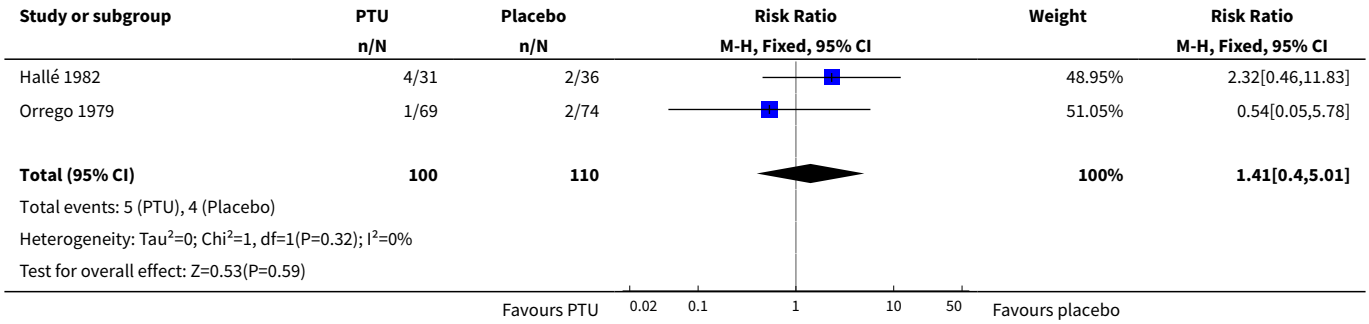
Comparison 2. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	2	210	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.28, 10.03]
2 Non-serious adverse events	2	210	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.40, 5.01]

Analysis 2.1. Comparison 2 Adverse events, Outcome 1 Serious adverse events.



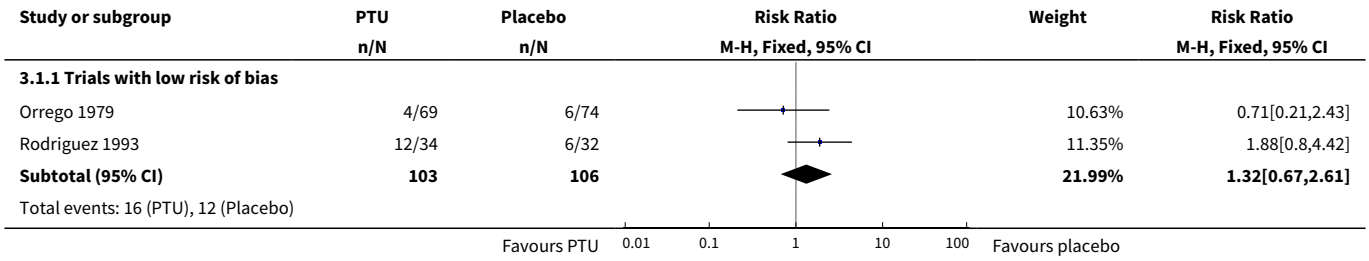
Analysis 2.2. Comparison 2 Adverse events, Outcome 2 Non-serious adverse events.

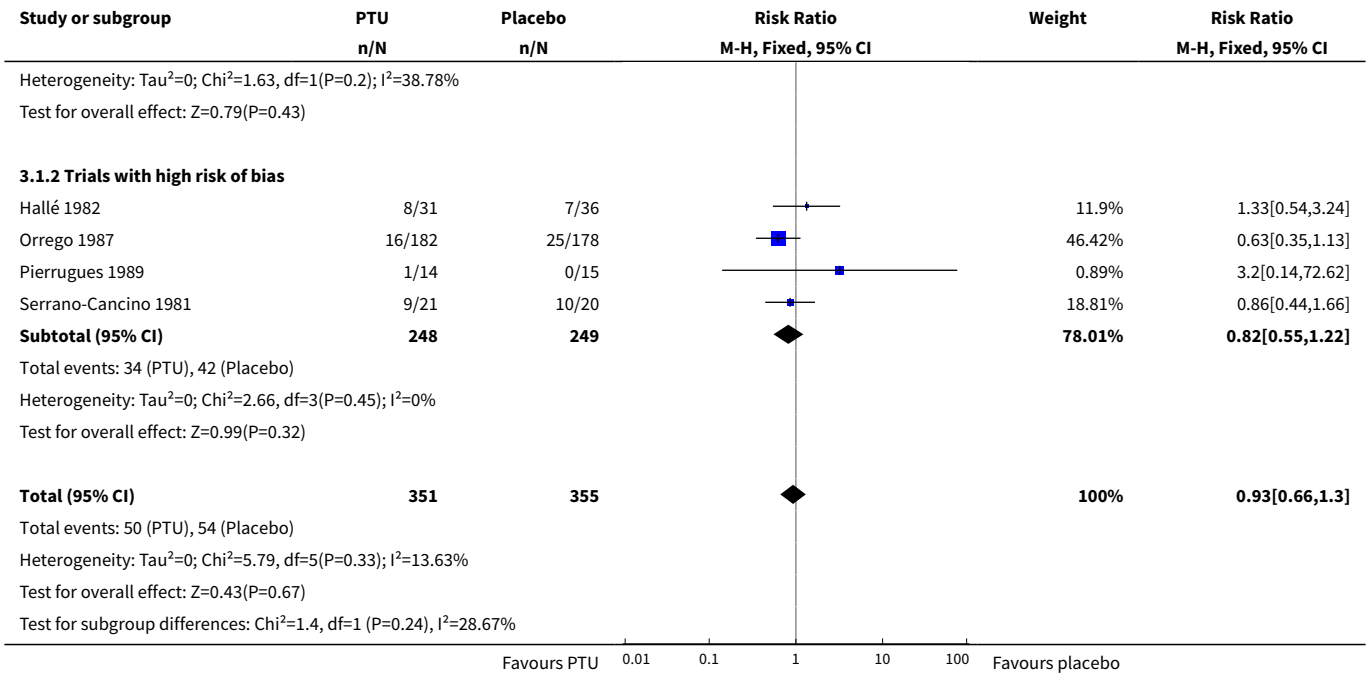


Comparison 3. Sensitivity analyses

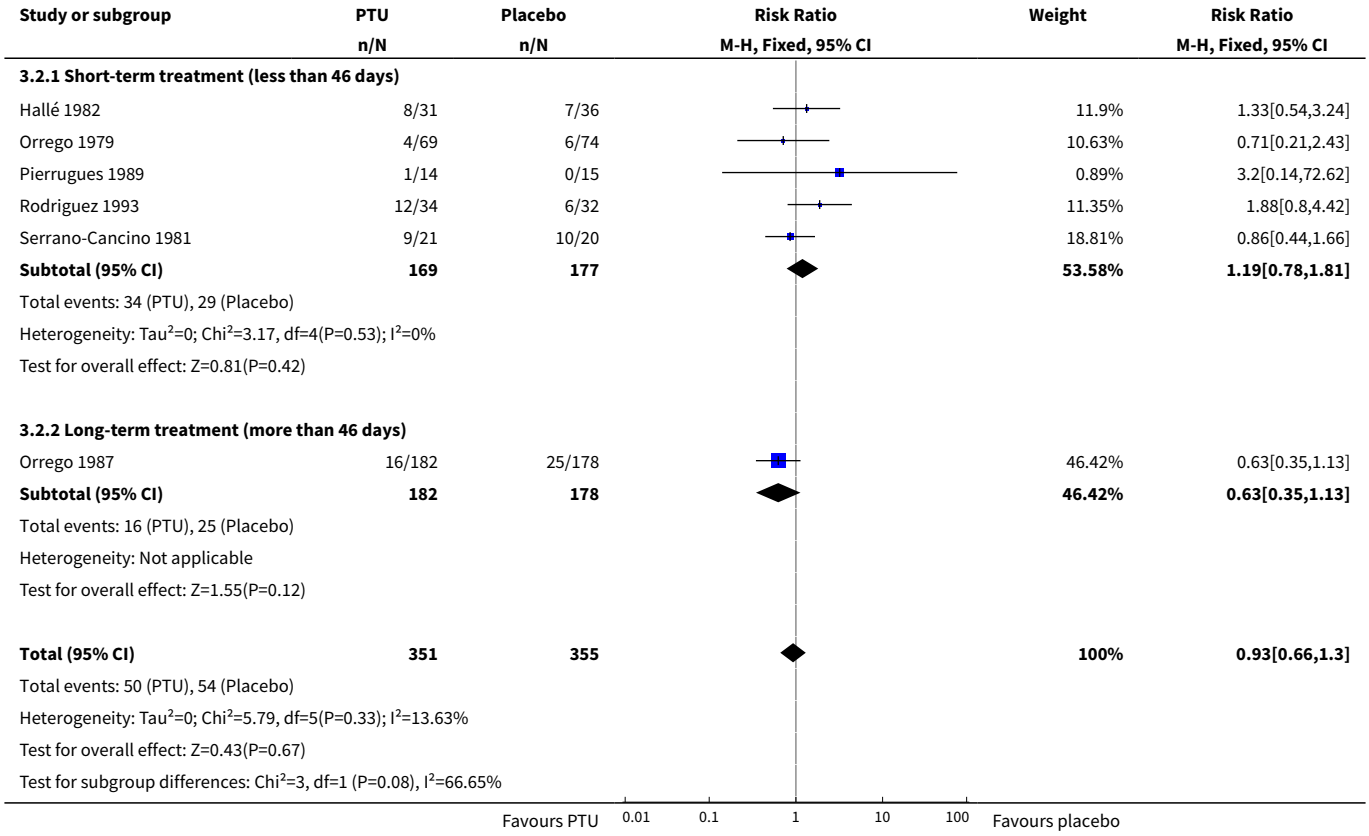
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality and quality criteria	6	706	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.66, 1.30]
1.1 Trials with low risk of bias	2	209	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.67, 2.61]
1.2 Trials with high risk of bias	4	497	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.55, 1.22]
2 Mortality and duration of treatment	6	706	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.66, 1.30]
2.1 Short-term treatment (less than 46 days)	5	346	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.78, 1.81]
2.2 Long-term treatment (more than 46 days)	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.35, 1.13]
3 Mortality and worst-best case scenario	6	706	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.70, 1.35]
4 Mortality and per-protocol analysis	6	646	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.63, 1.30]

Analysis 3.1. Comparison 3 Sensitivity analyses, Outcome 1 Mortality and quality criteria.

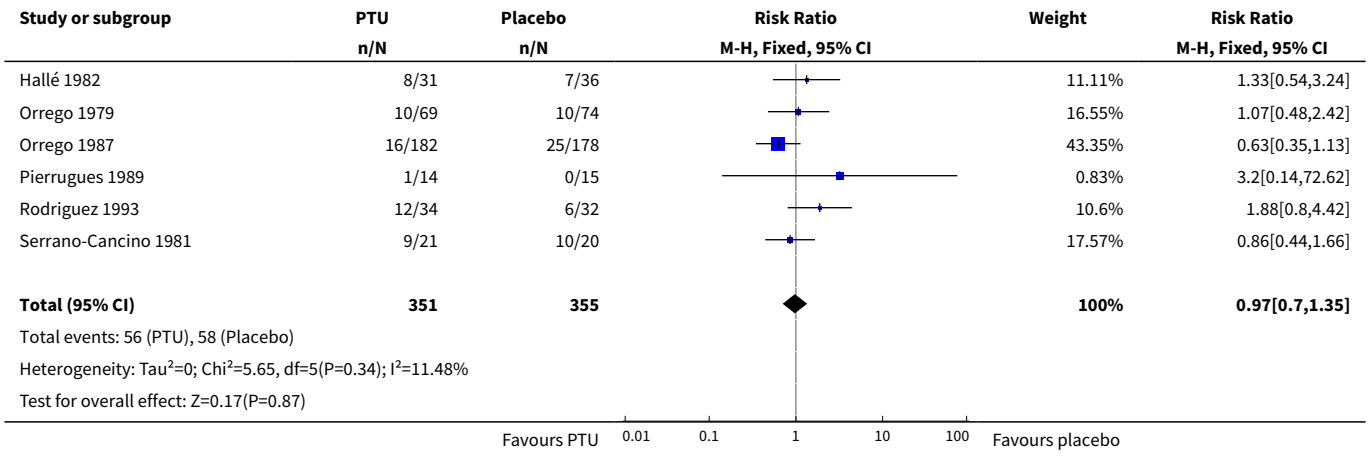




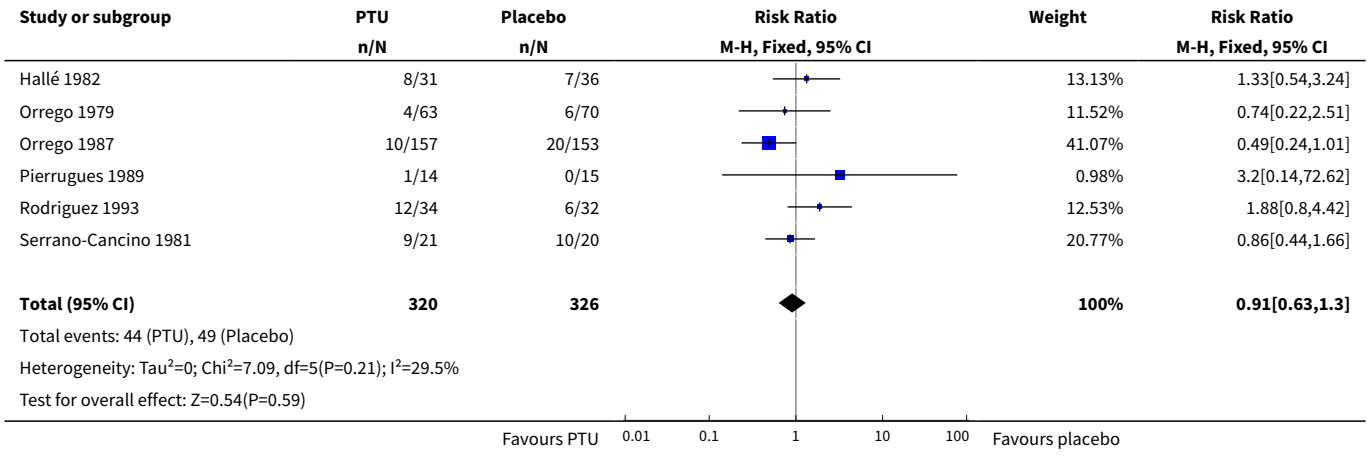
Analysis 3.2. Comparison 3 Sensitivity analyses, Outcome 2 Mortality and duration of treatment.



Analysis 3.3. Comparison 3 Sensitivity analyses, Outcome 3 Mortality and worst-best case scenario.



Analysis 3.4. Comparison 3 Sensitivity analyses, Outcome 4 Mortality and per-protocol analysis.



APPENDICES

Appendix 1. Search strategies

Database	Time of search	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	April 2011	propylthiouracil OR PTU
Cochrane Central Register of Controlled Trials	Issue 2, April 2011	#1 MeSH descriptor Propylthiouracil explode all trees in MeSH products #2 propylthiouracil OR PTU in All Fieldsin all products

(Continued)

(CENTRAL) in The Cochrane Library (Wiley)		#3 (#1OR #2) #4 MeSH descriptor Liver Diseases, Alcoholic explode all trees in MeSH products #5 alcoholic and (liver disease* or steatosis or fibrosis or hepatitis or cirrhosis) in All Fields in all products #6 (#4 OR #5) #7 (#3 AND #6)
MEDLINE (Ovid SP)	1948 to April 2011	#1 exp Propylthiouracil/ #2 (propylthiouracil or PTU).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] #3 1 or 2 #4 exp Liver Diseases, Alcoholic/ #5 (alcoholic and (liver disease* or steatosis or fibrosis or hepatitis or cirrhosis)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] #6 4 or 5 #7 3 and 6 #8 (random* or placebo* or blind* 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] #9 7 and 8
EMBASE (OvidSP)	1980 to April 2011	#1 exp PROPYLTHIOURACIL/ #2 (propylthiouracil or PTU).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] #3 1 or 2 #4 exp alcohol liver disease/ #5 (alcoholic and (liver disease* or steatosis or fibrosis or hepatitis or cirrhosis)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] #6 4 or 5 #7 3 and 6 #8 (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] #9 7 and 8
Science Citation Index Expanded (ISI Web of Knowledge)	1900 to April 2011	#1 TS=(propylthiouracil or PTU) #2 TS=(alcoholic and (liver disease* or steatosis or fibrosis or hepatitis or cirrhosis)) #3 #2 AND #1 #4 TS=(random* or placebo* or blind* or meta-analysis)

(Continued)

	#5 #4 AND #3

WHAT'S NEW

Date	Event	Description
28 January 2011	New citation required but conclusions have not changed	Conclusions did not change. No new trials were found for inclusion.
22 January 2011	New search has been performed	1. We changed the reporting of Peto odds ratio (OR) to relative risk (RR) as the latter is more easily understood. 2. We removed the Jadad scoring system for evaluation of trial quality since methodological quality is better evaluated by bias risk domains. 3. We now use both random-effects and fixed-effect models to analyse our data following the most recent guidelines.
21 January 2011	New search has been performed	New team of authors.

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 4, 2001

Date	Event	Description
23 August 2005	New search has been performed	Conclusions changed.

CONTRIBUTIONS OF AUTHORS

GF identified trials, extracted data, analysed the data, drafted the review. GG performed second data extraction. CG and KG made critical comments. AKB checked and revised all these processes.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Denmark.

External sources

- The Danish Medical Research Council Grant on Getting Research into Practice (GRIP), Denmark.
- The 1991 Pharmacy Foundation, Denmark.
- Copenhagen Hospital Corporation' Research Grant on Getting Research into Practice (GRIP), Denmark.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between current updated review and previous version

The methodological quality of the randomised clinical trials and type of outcomes were assessed using recent published recommendations (Gurusamy 2009; Higgins 2011).

NOTES

We have contacted Merck Frosst Canada Inc, Kirkland, Quebec (Canada) in order to obtain additional data, published or unpublished.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimetabolites [*therapeutic use]; Cause of Death; Liver Diseases, Alcoholic [*drug therapy] [mortality]; Propylthiouracil [*therapeutic use]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Humans