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Radix Sophorae flavescentis versus antiviral drugs for chronic hepatitis B (Protocol)

Liang N, Kong DZ, Nikolova D, Jakobsen JC, Gluud C, Liu JP

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[Intervention Protocol]

Radix Sophorae flavescentis versus antiviral drugs for chronic hepatitis B

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of Radix Sophorae flavescentis versus antiviral drugs in people with chronic hepatitis B.

BACKGROUND

Description of the condition

Hepatitis B is a liver disease caused by hepatitis B virus. Hepatitis B virus belongs to the *Hepadnaviridae* family of small, enveloped, primarily hepatotropic DNA viruses and is commonly classified into 10 genotypes (A through to J) (Sunbul 2014; Tong 2016). Hepatitis B virus is spread through percutaneous and mucosal exposure to blood and other body fluids such as semen and saliva of people infected with hepatitis B virus (Hou 2005; WHO 201). Despite that vaccination against hepatitis B virus has substantially reduced the number of newborns with mother-to-child transmission of hepatitis B infection (Goldstein 2005; Lee 2006; WHO 201; WHO 2017), in 2015, there were approximately 257 million people around the world, or 3.5% of the world's population, infected with hepatitis B virus (WHO 2017). In 2015, the estimated prevalence of hepatitis B virus infection was highest in Africa and the Western Pacific regions (WHO 2017). About 20% to 30% of chronically infected people can develop complications such as cirrhosis or hepatocellular carcinoma (WHO 201). In 2015, 880,000 people may die because of chronic hepatitis B virus infection (WHO 2017). People with hepatitis B infection may also have coinfections including HIV and other hepatitis viruses (hepatitis C and D) (Derikx 2011; Mallet 2017), and the coinfections may increase the risk of all-cause mortality (Puoti 2000; Mallet 2017). Chronic hepatitis B infection is a substantial economic, psychological, and life burden for the infected people and their families (Alizadeh 2008; Lu 2013; Keshavarz 2015; Ezbarami 2017).

The initial evaluation of people with chronic hepatitis B virus infection includes a thorough history, physical examination, assessment of liver disease activity and severity (e.g. liver biopsy, abdominal hepatic ultrasound, and alanine transaminase assessments), and markers of hepatitis B virus infection (e.g. HBV-DNA and hepatitis B virus e antigen (HBeAg)) (Pellicelli 2008; Jones 2009; Shepherd 2009; AASLD 2016; Wang 2016; EASL 2017). An immunological cure may be defined as HBeAg loss and sustained HBV-DNA suppression, and a virological cure may be defined as eradication of the virus in the blood, including the covalently closed circular DNA (cccDNA) form (EASL 2017). Reducing mortality and hepatitis B-related morbidities such as liver cirrhosis, liver failure, and liver cancer; prolonging survival; and improving quality of life are the main goals of chronic hepatitis B treatment (EASL 2012; WHO 201; EASL 2017).

Description of the intervention

Sophora is a genus of the Febaceae family, which includes several medicinal plants distributed in Asia, Oceanica, and the Pacific islands (Krishna 2012). *Sophora flavescens Aiton*, a perennial shrub, has been used in traditional medicine for centuries in China, Japan, and Korea (Tanabe 2015). Radix Sophorae flavescentis (Chinese name: Kushen) is the dried root of the shrub. It has been claimed that Radix Sophorae flavescentis has antibacterial, antiviral, anti-inflammatory, antitumour, and antipyretic effects and is one of the commonly used traditional Chinese medicinal remedies for chronic hepatitis B (Zhu 1998; Tanabe 2015). The extracts of Radix Sophorae flavescentis are dispensed as tablets, capsules, and injections (Long 2004; Mao 2004; Zhu 2009; Zou 2009). The treatment period usually ranges from one month to 24 months (Yin 2011; Lu 2012; Zhang 2012a; Lai 2015; Wang 2015; Wang 2017).

Certain adverse events such as abdominal pain, diarrhoea, nausea, vomiting, and fever have been reported to be likely associated with Radix Sophorae flavescentis (Gong 2000; Gu 2008; Zhang 2008; Li 2011; Li 2015).

How the intervention might work

The Chinese Pharmacopoeia reads that Radix Sophorae flavescentis is used to remove heat and damp from the body, and that it can be used for treating hepatitis and liver fibrosis (Chinese Pharmacopoeia 2015). Modern phytochemical studies have identified several active ingredients from Radix Sophorae flavescentis (Krishna 2012), among which matrine ($C_{15}H_{24}N_2O$) and oxymatrine ($C_{15}H_{24}N_2O_2$) are the main components (Liu 2003a). Animal studies have suggested that matrine may prevent liver fibrogenesis by inhibiting platelet derived growth factor (PDGF) synthesis and the transforming growth factor beta-1 (TGF-β1) proliferation (Zhang 2001), and matrine may inhibit hepatitis B virus replication by increasing Th1 cytokines and decreasing Th2 cytokines to trigger immune responses (Dong 2002). Studies in vitro have found that matrine is associated with anticancer action by inhibiting telomerase and tumour proliferation, preventing tumour cell invasion, and inducing tumour cell apoptosis (Qin 2009; Li 2017). Oxymatrine may inhibit hepatitis B virus replication by interfering with the process of packaging pregenomic ribonucleic acid (RNA) into the nucleocapsid, or by inhibiting viral DNA polymerase activity (Xu 2010).

Why it is important to do this review

We identified two meta-analyses on Radix Sophorae flavescentis for chronic hepatitis B (Liu 2003b; Wang 2017). Liu 2003b reported that Radix Sophorae flavescentis might decrease the proportion of participants with positive HBeAg and HBV-DNA, and might improve the survival of people with severe chronic hepatitis B. However, this included only 22 small randomised clinical trials, and all trials had low methodological quality based on the Jadad score (Jadad 1996; Liu 2003b). Only one of the included randomised trials reported mortality and showed that oxymatrine plus hepatocyte growth factor in addition to basic treatment reduced mortality compared with basic treatment alone (36.4% (8/22) with combination versus 73.3% (11/15) with basic treatment alone) (Liu 2003b). The trial design did not allow us to decide if it was oxymatrine or hepatocyte growth factor or the combination of the two that may have been responsible for the observed effect. The meta-analysis by Wang 2017 included nine randomised trials exploring the effects of Radix Sophorae flavescentis plus interferon versus interferon alone for chronic hepatitis B, and the combination therapy showed a better effect on reduction of HBV-DNA, HBeAg, and alanine aminotransferase (ALT) levels and development of anti-HBeAg antibodies (Wang 2017). The authors did not report on mortality (Wang 2017).

Previously published randomised clinical trials (Zou 2003; Yin 2011; Lu 2012; Zhang 2012a; Zhang 2012b; Lai 2015; Wang 2015), as well as the two meta-analyses (Liu 2003b; Wang 2017), primarily focused on assessing the effects of Radix Sophorae flavescentis on surrogate outcomes. It is questionable whether these surrogate outcome results lead to improvement in clinically important outcomes because validation of any association should be carried out in randomised clinical trials (Gluud 2007; Fleming 2012; Ciani 2017; Jakobsen 2017; Kemp 2017; Jakobsen 2018). The clinical benefits and harms of Radix Sophorae flavescentis remain vague. Before assessing benefits and harms of any intervention versus another, the benefits and harms versus placebo or no intervention need to be established (Jakobsen 2013). This is why we have planned two reviews: Radix Sophorae flavescentis versus placebo or no intervention for chronic hepatitis B (Liang 2018) and this current one (Radix Sophorae flavescentis versus antiviral drugs for chronic hepatitis B).

OBJECTIVES

To assess the benefits and harms of Radix Sophorae flavescentis versus antiviral drugs in people with chronic hepatitis B.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of blinding, language, year, publication format, and publication status. We will also consider quasi-randomised studies, controlled clinical studies, and other observational studies for data on harms if retrieved with our searches for randomised clinical trials. This is because adverse events are rarely reported in randomised clinical trials (Storebø 2018). Moreover, observational studies may provide information on rare or late-occurring adverse events (Storebø 2018). We are aware that the decision not to search for all observational studies may bias our review towards assessment of benefits and may overlook certain harms such as late or rare harms.

Types of participants

Inclusion criteria

Trial participants of any sex and age, diagnosed with chronic hepatitis B, as defined by trialists or according to guidelines (HBeAg positivity for more than six months, serum HBV-DNA positivity more than 2000 IU/mL (i.e. more than 10^4 copies/mL), persistent or intermittent elevation in levels of aspartate aminotransferase (AST) or ALT, and liver biopsy findings showing chronic hepatitis B with moderate or severe necroinflammation) (AASLD 2016; EASL 2017).

In addition to chronic hepatitis B, trial participants may also have cirrhosis, hepatocellular carcinoma, concomitant HIV infection or AIDS, hepatitis C, hepatitis D, or any other concomitant disease.

Exclusion criteria

None.

Types of interventions

Experimental intervention

Radix Sophorae flavescentis or its extractions (e.g. matrine, oxymatrine) at any dose, form, or regimen. We will not consider polyherbal blends containing Radix Sophorae flavescentis because it will not allow us to decide whether the observed effect was in association with Radix Sophorae flavescentis or with other herbs.

Control intervention

Antiviral drugs either recommended in guidelines (interferon, lamivudine, adefovir, entecavir, telbivudine, tenofovir, and emtricitabine) (EASL 2012; AASLD 2016; EASL 2017), or commonly used drugs in clinical practice with potential antiviral effect (e.g. *Phyllanthus* species) (Xia 2011; Xia 2013).

We will allow cointerventions in the experimental and control intervention groups provided that the cointerventions were administered equally to all the intervention groups of a trial.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Proportion of participants with one or more serious adverse events; that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect (ICH-GCP 1997).
- Health-related quality of life: any scale used by trialists to assess the participants' reporting of their quality of life.

Secondary outcomes

- Hepatitis B-related mortality.
- Hepatitis B-related morbidity (proportion of participants with one or more of the following events: cirrhosis, ascites, variceal bleeding, hepato-renal syndrome, hepatocellular carcinoma, hepatic encephalopathy, or needed liver transplantation, and who have not died).
- Proportion of participants with one or more non-serious adverse events: any untoward medical occurrence in a participant that does not meet the above criteria for a serious adverse event is defined as a non-serious adverse event (ICH-GCP 1997).

Exploratory outcomes

- Proportion of participants with detectable HBV-DNA in serum, plasma, or HBV-DNA viral load.
- Proportion of participants with detectable HBeAg in serum or plasma.
- Separately reported serious adverse events.
- Separately reported hepatitis B-related morbidity.

- Separately reported non-serious adverse events.

We will assess all outcomes at maximal follow-up.

Search methods for identification of studies

Electronic searches

We will search The Cochrane Hepato-Biliary Group Controlled Trials Register (Cochrane Hepato-Biliary Group Module), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Bireme), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index-Science (Web of Science) (Royle 2003). We will also search four Chinese biomedical databases: China Network Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), Wanfang Data, and SinoMed.
Appendix 1 provides the preliminary search strategies with the expected time spans for the searches.

Searching other resources

We will search the reference lists of meta-analyses on this topic and of the retrieved studies. We will also search the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp), ClinicalTrials.gov (www.clinicaltrials.gov/), and the Chinese Clinical Trial Registry (ChiCTR) for ongoing or unpublished trials.

Data collection and analysis

We will conduct our review according to the guidelines of *The Cochrane Handbook for Systematic Reviews of Interventions*, and the Cochrane Hepato-Biliary Group Module.
We will perform analyses using Review Manager 5 (Review Manager 2014), and Trial Sequential Analysis version 0.9.5.10 Beta software (Thorlund 2011a; TSA 2011).

Selection of studies

Review authors in pairs will independently screen titles and abstracts for inclusion of potentially eligible trials. We will list multiple reports of the same trial under their main reference. We will list ineligible studies with reasons for exclusion in 'Excluded studies.' We will resolve any disagreements through discussion, or we will ask JPL to arbitrate. We will record the selection process in a PRISMA flow diagram (PRISMA 2009).

Data extraction and management

Review authors in pairs will independently extract data using a prepiloted electronic data collection form created in Microsoft Excel. In case of discrepancies, we will recheck the extracted data. If disagreements persist, we will try to resolve any disagreements through discussion. We will contact JPL to arbitrate if disagreements still exist, before proceeding with the analyses.
We will extract the following information: publication data (i.e. year, country, authors); study characteristics and design; characteristics of trial participants; trial inclusion and exclusion criteria; interventions; outcomes; follow-up; and types of data analyses (i.e. intention-to-treat, modified intention-to-treat, per protocol). If data are missing in the reports, we will contact the trial authors for the missing information. We will extract data at maximum follow-up.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in the included trials. We will assess risk of bias according to the Cochrane 'Risk of bias' tool (Higgins 2011), the Cochrane Hepato-Biliary Group Module, and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017; Savović 2018), using the following sources of bias, defined as follows.

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person, not otherwise involved in the study, performed them.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We will only include such studies for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We will only include such studies for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: either of the following: blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken; or rarely no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding such as mortality.
- Unclear risk of bias: either of the following: insufficient information to permit judgement of low risk or high risk; or the study did not address this outcome.
- High risk of bias: either of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessment

- Low risk of bias: either of the following: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or rarely no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding such as mortality.
- Unclear risk of bias: either of the following: insufficient information to permit judgement of low risk or high risk; or the study did not address this outcome.
- High risk of bias: either of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data, in combination with the method used to handle missing data, were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: all predefined, or clinically relevant and reasonably expected, outcomes were reported. If the original study protocol was available, the outcomes should have been those called for in that protocol. (Note: if the study protocol was obtained from a study registry (e.g. www.clinicaltrials.gov), the outcomes sought were those enumerated in the original protocol, if the study protocol was registered before, or at the time that the study began; if the study protocol was registered after the study began, those outcomes will not be considered to be reliable in representing the outcomes initially being sought.) If the study protocol was not available (or if the protocol was registered after the study began), then we will assess for reports of all-cause mortality, serious adverse events, and health-related quality of life outcomes, as we deem these to be the most clinically relevant and reasonably expected outcomes.
- Unclear risk of bias: the study authors did not report all predefined outcomes fully, or it was unclear whether the study authors recorded data on these outcomes or not.
- High risk of bias: the study authors did not report one or more predefined outcomes.

For-profit bias

- Low risk of bias: the study appeared to be free of industry sponsorship or other type of for-profit support that could manipulate the study design, conductance, or results of the study (industry-sponsored studies overestimate the efficacy by about 25%) (Lundh 2017).
- Unclear risk of bias: the study may or may not have been free of for-profit bias as the study did not provide any information on clinical study support or sponsorship.
- High risk of bias: the study was sponsored by industry or received another type of for-profit support (Lundh 2017).

Other bias

- Low risk of bias: the study appeared to be free of other factors that could put it at risk of bias.
- Unclear risk of bias: the study may or may not have been free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the study that could put it at risk of bias.

Overall risk of bias

- Low risk of bias: the outcome result will be classified as at overall low risk of bias only if all of the risk of bias sources described above are classified as at low risk of bias.
- High risk of bias: the outcome result will be classified as at overall high risk of bias if any of the risk of bias sources described above are classified as at unclear risk of bias or high risk of bias.

We will try to reach consensus through discussion. We will contact JPL to arbitrate if disagreements still exist.
Our primary conclusions will be based on the results of all our primary and secondary outcome results with overall low risk of bias.

Measures of treatment effect

We will use the risk ratios (RR) for measuring dichotomous outcomes and mean differences (MD) for continuous data with 95% confidence intervals (CI) for head-to-head comparison meta-analysis. When studies use different instruments to measure the same continuous outcome, we will calculate the standardised mean difference (SMD) with 95% CI.

Unit of analysis issues

We will follow the guidelines set in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The unit of analysis will be the participants randomised into the trial intervention groups. For trials with multiple intervention groups, we will only include the groups in which our experimental and control interventions are compared. If the control intervention group is a common comparator for two or more experimental intervention groups, then we will divide the control group into two in order to avoid double-counting.

For cluster-randomised trials, we will directly extract data from the analysis that properly accounts for the cluster design. If control of clustering has not been performed, we will determine the inflated standard errors, which account for clustering, entering them into Review Manager 5 under a generic inverse-variance outcome (Higgins 2011; Review Manager 2014).

For cross-over trials, we will extract only data from the first period to avoid residual treatment effects (Higgins 2011).

Dealing with missing data

We will attempt to contact trial authors for missing data or information that is not clearly presented.

We will perform our analysis using the intention-to-treat method whenever possible. If not possible, we will use the data that are available to us. For all primary and secondary outcomes, we will include participants with incomplete or missing data in the sensitivity analyses by imputing them as follows.

For dichotomous outcomes:

- best- and worst-case scenario: assumes that all participants lost to follow-up in the experimental group have survived, have improvement in clinical symptoms, have no serious adverse event, and have no morbidity (for all dichotomous variables); and that all participants lost to follow-up in the control group have not survived, have no improvement in clinical symptoms, have a serious adverse event, and have morbidities (for all dichotomous variables);
- worst- and best-case scenario: assumes that all participants lost to follow-up in the experimental group have not survived, have no improvement in clinical symptoms, have a serious adverse event, and have morbidities (for all dichotomous variables); and that all participants lost to follow-up in the control group have survived, have improvement in clinical symptoms, have no serious adverse event, and have no morbidity (for all dichotomous variables).

For continuous outcomes:

- we will base the 'beneficial' outcome on the group mean plus two standard deviations (SDs), or one SD, and the 'harmful' outcome on the group mean minus two SDs, or one SD (Jakobsen 2014).

If SDs are not reported, we will request the information from trial authors, or we will calculate them using data from the trial, if possible.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the trial participant characteristics and design of included trials. We will assess the presence of clinical heterogeneity by comparing effect estimates (see Subgroup analysis and investigation of heterogeneity) in trial reports in terms of participants with different diagnostic criteria, participants diagnosed with only chronic hepatitis B and participants diagnosed with concomitant diseases, different duration and dosages of the intervention, cointerventions, different control interventions, and follow-up. Different study designs and risk of bias can contribute to methodological heterogeneity. We will assess statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis. We will start by looking at the forest plots for signs of statistical heterogeneity. Next, we will use the Chi² test with significance threshold set as $P < 0.10$, and measure the amount of heterogeneity using the I^2 statistic to assess to what extent heterogeneity is present (Higgins 2002; Higgins 2003; Higgins 2011). An approximate guide of I^2 is as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity (Higgins 2011).

If the statistical heterogeneity is substantial (i.e. I^2 greater than 50%), we will try to explore and discuss the possible reasons for it, and will perform subgroup analyses based on our reasoning. If the I^2 statistic is higher than 75%, we will present the data analysis in a narrative way, rather than perform data synthesis through meta-analysis.

For the heterogeneity adjustment of the required information size (RIS) in the Trial Sequential Analysis, we will use diversity (D^2) because the I^2 statistic used for this purpose may underestimate the RIS (Wetterslev 2009).

Assessment of reporting biases

We will assess reporting bias using funnel plots if we have data from at least 10 trials per comparison. To assess bias risk, we will look for symmetry or asymmetry of each funnel plot. For dichotomous outcomes, we will assess asymmetry using the Harbord test

(Harbord 2006). For continuous outcomes, we will apply the regression asymmetry test (Egger 1997).

Data synthesis

Meta-analysis

We will perform the analyses following the instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module. We will analyse data with Review Manager 5 (Review Manager 2014).

We will assess our intervention effects with both fixed-effect model and random-effects model meta-analyses, and we will report both results if results differ (e.g. one giving a significant intervention effect, the other no significant intervention effect). We will primarily put more weight on the estimate closest to zero effect (the highest P-value) (Jakobsen 2014).

We will assess the three primary outcomes with a P value of 0.025 or less as significant, and the three secondary outcomes with a P value of 0.025 or less as significant, to secure a family-wise error rate below 0.05 (Jakobsen 2014). For the exploratory outcomes, we will consider a P value less than 0.05 as significant because we view these outcomes as only hypothesis-generating outcomes. Whether we shall present our data synthesis as a meta-analysis or in a narrative way, will depend on our assessment of the statistical and clinical heterogeneity of the meta-analysed trial data per comparison.

We will not impute any missing data in our primary analysis; however, we will impute missing values in our sensitive analysis of continuous and dichotomous data (see Sensitivity analysis) (Jakobsen 2014).

If data are available from only one trial, we will use Fisher's exact test for dichotomous data (Fisher 1922) and Student's t-test for continuous data (Student 1908).

Trial Sequential Analysis

As cumulative meta-analysis contains a risk of producing random errors due to sparse data and repetitive testing, we will perform Trial Sequential Analysis. To minimise random errors, we will calculate the RIS (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Wetterslev 2008; Thorlund 2011a; TSA 2011). The diversity-adjusted required information size (DARIS) calculation should also account for the diversity present in the meta-analysis (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). A more detailed description of Trial Sequential Analysis can be found at www.ctu.dk/tsa (Thorlund 2011a; TSA 2011). We will control the risks of type I errors and type II errors for both dichotomous and continuous outcomes (Brok 2008; Wetterslev 2008; Brok 2009; Wetterslev 2009; Thorlund 2010; Castellini 2017; Wetterslev 2017). For dichotomous outcomes, we will estimate the DARIS based on the event proportion in the control group of the meta-analysis, a relative risk reduction of 15%, an alpha of 2.5% for primary and secondary outcomes, 5.0% for exploratory outcomes, a beta of 10% (Castellini 2017), and diversity suggested by the trials in the meta-analysis (Wetterslev 2009; Jakobsen 2014). For continuous outcomes, we will estimate the DARIS based on the SD observed in the control group, a minimal relevant difference of 50% of this SD, an alpha of 2.5%, a beta of 10% (Castellini 2017), and diversity suggested by the trials in the meta-analysis (Wetterslev 2009; Jakobsen 2014).

We will test statistical significance and futility using 'trial sequential monitoring boundaries' for benefit, harm, and futility (Thorlund 2011a). If the Z-curve crosses the trial sequential monitoring boundaries for benefit or harm before reaching DARIS, the effect of the intervention will be considered superior or inferior to the control intervention. In contrast, a Z-curve crossing the futility boundaries before reaching the DARIS would mean that the intervention does not possess the postulated effect and further randomisation of trial participants may be futile. If the sequential monitoring boundaries are not surpassed and the trial monitoring boundaries for futility are not crossed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect (Wetterslev 2008; Thorlund 2011b). In case the monitoring boundaries are reached, we will also display the Trial Sequential Analysis-adjusted CI.

Subgroup analysis and investigation of heterogeneity

If data are available, we will perform the following subgroup analyses:

- trials at low risk of bias compared to trials at high risk of bias;
- trials at low risk of bias compared to trials at high risk of bias on blinding of outcome assessment;
- trials at low risk of bias compared to trials at high risk of bias on incomplete outcome data;
- trials at low risk of bias compared to trials at high risk of bias on selective outcome reporting;
- different administration ways of Radix Sophorae flavescentis;
- different dosage and duration of the intervention stratified according to the medians observed;
- different antiviral drugs in the control group;
- participants according to different diagnostic criteria;
- participants diagnosed only with chronic hepatitis B compared to participants diagnosed with concomitant diseases (cirrhosis, hepatocellular carcinoma, HIV infection, AIDS, hepatitis C, hepatitis D, or a combination of these). We will try to analyse each concomitant disease separately.

Sensitivity analysis

In addition to the sensitivity analysis described in Dealing with missing data, we will also explore imprecision in sensitivity analysis, using Trial Sequential Analysis, as described by Jakobsen 2014. We may conduct further sensitivity analyses during the review process if we need to test further the robustness of conclusions. We will report this in the 'Differences between protocol and review' section of the review.

'Summary of findings' table

We will construct 'Summary of findings' tables in order to determine our confidence in the evidence on all primary outcomes (all-cause mortality, proportion of participants with one or more serious adverse events, health-related quality of life) and all secondary outcomes (hepatitis B-related mortality, hepatitis B-related morbidity, proportion of participants with one or more non-serious adverse events), and we will show our results per outcome. We will display information of assumed control group risk, corresponding intervention group risk, relative effect, MD, CI, statistical significance of relative effect, number of participants, and quality of the evidence. The corresponding risk (and its 95% CI) is calculated using the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Using GRADEpro GDT software (GRADEpro GDT), we will assess five factors of the evidence referring to limitations in the study design and implementation that suggest the quality of evidence: within-study risk of bias, indirectness of the evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses), imprecision of results, and risk of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Mustafa 2013; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; GRADEpro GDT; Guyatt 2017).
The evidence grades are defined as follows.

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

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REFERENCES

Additional references

AASLD 2016
Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology (Baltimore, Md.)* 2016;**63**(1):261–83.

Alizadeh 2008
Alizadeh AHM, Ranjbar M, Yadollahzadeh M. Patient concerns regarding chronic hepatitis B and C infection. *Eastern Mediterranean Health Journal* 2008;**14**(5):1142–7.

Balshem 2011
Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401–6.

Brok 2008
Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 2008;**61**(8):763–9.

Brok 2009
Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):287–98.

Castellini 2017
Castellini G, Nielsen EE, Gluud C. Comment on: "Cell therapy for heart disease: trial sequential analyses of two Cochrane Reviews". *Clinical Pharmacology and Therapeutics* 2017;**102**:21–4.

Chinese Pharmacopoeia 2015
The Tenth Pharmacopoeia Commission. *The Pharmacopoeia of People's Republic of China*. 10th Edition. Beijing (CN): China Medical Science Press, 2015.

Ciani 2017
Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS. Time to review the role of surrogate end points in health policy: state of the art and the way forward. *Value Health* 2017;**20**(3):487–95.

Derikx 2011
Derikx MH, Spanier BW, Vrolijk JM. Hepatitis B; sometimes co-infection with hepatitis D [Hepatitis B; soms ook samen met hepatitis D]. *Nederlands Tijdschrift voor Geneeskunde* 2011;**155**:A3513.

Dong 2002
Dong Y, Xi H, Yu Y, Wang Q, Jiang K, Li L. Effects of oxymatrine on the serum levels of T helper cell 1 and 2 cytokines and the expression of the S gene in hepatitis B virus S gene transgenic mice: a study on the anti-hepatitis B virus mechanism of oxymatrine. *Journal of Gastroenterology and Hepatology* 2002;**17**(12):1299–306.

EASL 2012
European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *Journal of Hepatology* 2012;**57** (1):167–85.

EASL 2017
European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *Journal of Hepatology* 2017;**67** (2):370–98.

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

Ezbarami 2017
Ezbarami ZT, Hassani P, Tafreshi MZ, Majd HA. A qualitative study on individual experiences of chronic hepatitis B patients. *Nursing Open* 2017;**4**(4):310–8.

Fisher 1922
Fisher RA. On the interpretation of X^2 from contingency tables, and the calculation of P. *Journal of the Royal Statistical Society* 1922;**85**(1):87–94.

Fleming 2012
Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. *Statistics in Medicine* 2012;**31** (25):2973–84.

Gluud 2007
Gluud C, Brok J, Gong Y, Koretz RL. Hepatology may have problems with putative surrogate outcome measures. *Journal of Hepatology* 2007;**46**(4):734–42.

Goldstein 2005
Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *International Journal of Epidemiology* 2005;**34**(6):1329–39.

Gong 2000
Gong ZF. A case report of respiratory muscle paralysis caused by matrine. *Lishizhen Medicine and Materia Medica Research* 2000;**2**(5):466.

GRADEpro GDT [Computer program]
McMaster University (developed by Evidence Prime). GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Gu 2008
Gu JY. Allergic drug eruption caused by Kushensu. *Chinese Journal of Pharmacoepidemiology* 2008;**17**(1):61.

Guyatt 2011a
Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines: 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93. [PUBMED: 21839614]

Guyatt 2011b
Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence - publication bias. *Journal of Clinical Epidemiology* 2011;**64**(12):1277–82. [PUBMED: 21802904]

Guyatt 2011c
Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(12):1311–6. [PUBMED: 21802902]

Guyatt 2011d
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294–302. [PUBMED: 21803546]

Guyatt 2011e
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence - indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303–10. [PUBMED: 21802903]

Guyatt 2011f
Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology* 2011;**64**(4):395–400. [PUBMED: 21194891]

Guyatt 2011g
Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence - study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407–15. [PUBMED: 21247734]

Guyatt 2011h
Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE

evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383–94. [PUBMED: 21195583]

Guyatt 2013a

Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):151–7. [PUBMED: 22542023]

Guyatt 2013b

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables - binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158–72. [PUBMED: 22609141]

Guyatt 2013c

Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles - continuous outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):173–83. [PUBMED: 23116689]

Guyatt 2013d

Guyatt G, Andrews J, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 15. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of Clinical Epidemiology* 2013;**66**(7):719–25.

Guyatt 2017

Guyatt GH, Ebrahim S, Alonso-Coello P, Johnston BC, Mathioudakis AG, Briel M, et al. GRADE guidelines: 17. Assessing the risk of bias associated with missing participant outcome data in a body of evidence. *Journal of Clinical Epidemiology* 2017;**87**:14–22. [PUBMED: 28529188]

Harbord 2006

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

Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539–58.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical Research Ed.)* 2003;**327**(7414):557–60.

Higgins 2011

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

Hou 2005

Hou JL, Liu ZH, Gu F. Epidemiology and prevention of hepatitis B virus infection. *International Journal of Medical Sciences* 2005;**2**(1):50–7.

ICH-GCP 1997

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

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1–12.

Jakobsen 2013

Jakobsen JC, Gluud C. The necessity of randomized clinical trials. *British Journal of Medicine & Medical Research* 2013;**3** (4):1453–68.

Jakobsen 2014

Jakobsen J, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**:120. DOI: 10.1186/1471-2288-14-120

Jakobsen 2017

Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, et al. Direct-acting antivirals for chronic hepatitis C. *Cochrane Database of Systematic Reviews* 2017, Issue 9. DOI: 10.1002/14651858.CD012143.pub3

Jakobsen 2018

Jakobsen JC, Nielsen EE, Koretz RL, Gluud C. Do direct acting antivirals cure chronic hepatitis C?. *BMJ (Clinical Research Ed.)* 2018;**10**(361):k1382.

Jones 2009

Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, et al. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. *Health Technology Assessment* 2009;**13**(35):1–172.

Kemp 2017

Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused?. *BMC Medicine* 2017;**15**(1): 134.

Keshavarz 2015

Keshavarz K, Kebriaeezadeh A, Alavian SM, Sari AA, Dorkoosh FA, Keshvari M, et al. Economic burden of hepatitis B virus-related diseases: evidence from Iran. *Hepatitis Monthly* 2015;**15**(4):e25854.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982–9.

Krishna 2012

Krishna PM, Rao KN, Sandhya S, Banji D. A review on phytochemical, ethnomedical and pharmacological studies on genus Sophora, Febaceae. *Brazilian Journal of Pharmacognosy* 2012;**22**(5):1145–54.

Lai 2015
Lai WH. Lamivudine in combination with matrine for chronic hepatitis B. *Journal of Community Medicine* 2015; **13**(24):50–1.

Lee 2006
Lee CF, Gong Y, Jesper B, Boxall EH, Cluud C. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. *Cochrane Database of Systematic Reviews* 2006, Issue 2. DOI: 10.1002/14651858.CD004790.pub2

Li 2011
Li JL, Huang HL. Epidemiological characteristics of adverse reaction of oxymatrine on database analyze. *Anti-tumor Pharmacy* 2011;**1**(2):149–52.

Li 2015
Li XJ. One case of allergic shock caused by oxymatrine glucose injection. *Journal of Pharmaceutical Research* 2015; **34**(2):124.

Li 2017
Li Q, Wang LL, Xu J, Shang XH, Wang CB. Matrine for treatment of carcinoma. *International Journal of Laboratory Medicine* 2017;**38**(4):500–2.

Liang 2018
Liang N, Kong DZ, Nikolova D, Jakobsen JC, Gluud C, Liu JP. Radix Sophorae flavescentis for chronic hepatitis B. Cochrane Database of Systematic Reviews Under development (submitted June 2018).

Liu 2003a
Liu M, Liu XY, Cheng JF. Advance in the pharmacological research on matrine. *China Journal of Chinese Materia Medica* 2003;**28**(9):801–4.

Liu 2003b
Liu JP, Zhu MH, Shi R, Yang M. Radix Sophorae flavescentis for chronic hepatitis B: a systematic review of randomized trials. *American Journal of Chinese Medicine* 2003;**31**(3):337–54.

Long 2004
Long Y, Lin XT, Zeng KL, Zhang L. Efficacy of intramuscular matrine in the treatment of chronic hepatitis B. *Hepatobiliary & Pancreatic Diseases International* 2004;**3** (1):69–72.

Lu 2012
Lu XH. Telbivudine in combination with matrine injection for treating chronic hepatitis B. *Guide of China Medicine* 2012;**10**(33):483–4.

Lu 2013
Lu JJ, Xu AQ, Wang J, Zhang L, Song LZ, Li RP, et al. Direct economic burden of hepatitis B virus related diseases: evidence from Shandong, China. *BMC Health Services Research* 2013;**13**:37.

Lundh 2017
Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 2. DOI: 10.1002/14651858.MR000033.pub3

Mallet 2017
Mallet V, Hamed K, Schwarzinger M. Prognosis of patients with chronic hepatitis B in France (2008-2013): a nationwide, observational and hospital-based study. *Journal of Hepatology* 2017;**66**(3):514–20.

Mao 2004
Mao YM, Zeng MD, Lu LG, Wan MB, Li CZ, Chen CW, et al. Capsule oxymatrine in treatment of hepatic fibrosis due to chronic viral hepatitis: a randomized, double blind, placebo-controlled, multicenter clinical study. *World Journal of Gastroenterology* 2004;**10**(22):3269–73.

Moher 1998
Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? . *Lancet* 1998;**352**(9128):609–13.

Mustafa 2013
Mustafa RA, Santesso N, Brozek J, Akl EA, Walter SD, Norman G, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *Journal of Clinical Epidemiology* 2013;**66**(7):736-42; quiz 742.e1-5. [PUBMED: 23623694]

Pellicelli 2008
Pellicelli AM, Barbaro G, Francavilla R, Romano M, Barbarini G, Mazzoni E, et al. Adefovir and lamivudine in combination compared with adefovir monotherapy in HBeAg-negative adults with chronic hepatitis B virus infection and clinical or virologic resistance to lamivudine: a retrospective, multicenter, nonrandomized, open-label study. *Clinical Therapeutics* 2008;**30**(2):317–23.

PRISMA 2009
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical Research Ed.)* 2009;**339**:b2700. DOI: doi.org/10.1136/bmj.b2700

Puoti 2000
Puoti M, Spinetti A, Ghezzi A, Donato F, Zaltron S, Putzolu V, et al. Mortality for liver disease in patients with HIV infection: a cohort study. *Journal of Acquired Immune Deficiency Syndromes* 2000;**24**(3):211–7.

Qin 2009
Qin KM, Fang QB, Cai H, Cai BC. Summary of research on anticancer mechanism of constituent matrine. *Journal of Shenzhen Polytechnic* 2009;**8**(3):61–6.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Royle 2003
Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591–603.

Savović 2012a

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

Savović 2012b

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

Savović 2018

Savović J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JPT, et al. Association between risk-of-bias assessments and results of randomized trials in Cochrane Reviews: The ROBES Meta-Epidemiologic Study. *American Journal of Epidemiology* 2018;**187**(5):1113–22.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

Shepherd 2009

Shepherd J, Gospodarevskaya E, Frampton G, Cooper K. Entecavir for the treatment of chronic hepatitis B infection. *Health Technology Assessment* 2009;**13**(Suppl 3):31–6.

Storebø 2018

Storebø OJ, Pedersen N, Ramstad E, Kielsholm ML, Nielsen SS, Krogh HB, et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of adverse events in non-randomised studies. *Cochrane Database of Systematic Reviews* 2018, Issue 5. DOI: 10.1002/14651858.CD012069.pub2

Student 1908

Student. The probable error of a mean. *Biometrika* 1908;**6** (1):1–25.

Sunbul 2014

Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. *World Journal of Gastroenterology* 2014;**20**(18):5427–34.

Tanabe 2015

Tanabe N, Kuboyama T, Kazuma K, Konno K, Tohda C. The extract of roots of sophora flavescens enhances the recovery of motor function by axonal growth in mice with a spinal cord injury. *Frontiers in Pharmacology* 2015;**6**:326.

Thorlund 2010

Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. *Clinical Epidemiology* 2010;**2**:57–66.

Thorlund 2011a

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA), 2011. ctu.dk/tsa/files/tsa_manual.pdf (accessed 16 January 2017).

Thorlund 2011b

Thorlund K, Imberger G, Walsh M, Chu R, Gluud C, Wetterslev J, et al. The number of patients and events required to limit the risk of overestimation of intervention effects in meta-analysis - a simulation study. *PLoS One* 2011;**6**(10):e25491.

Tong 2016

Tong SP, Revill P. Overview of viral replication and genetic variability. *Journal of Hepatology* 2016;**64**(1 Suppl):S1–S16.

TSA 2011 [Computer program]

Copenhagen Trial Unit. TSA - Trial Sequential Analysis. Version 0.9.5.10 Beta. Copenhagen: Copenhagen Trial Unit, 2011.

Wang 2015

Wang HW, Hou LJ, Li WW, Duan SP, Shen BS, Song XW. Clinical analysis of entecavir combined with Kushensu in treatment of chronic hepatitis B. *China Continuing Medical Education* 2015;7(15):195–6.

Wang 2016

Wang HL, Lu X, Yang X, Xu N. Antiviral therapy in lamivudine-resistant chronic hepatitis B patients: a systematic review and network meta-analysis. Gastroenterology Research and Practice 2016; Vol. 2016: 3435965.

Wang 2017

Wang XT, Lin HX, Zhang R. The clinical efficacy and adverse effects of interferon combined with matrine in chronic hepatitis B: a systematic review and meta-analysis. *Phytotherapy Research* 2017;**31**(6):849–57.

Wetterslev 2008

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

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Medical Research Methodology* 2009;**9**:86.

Wetterslev 2017

Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology* 2017;**17**(1):39.

WHO 2017

World Health Organization. Global hepatitis report, 2017. www.who.int/hepatitis/publications/global-hepatitis-report2017/en/ (accessed 13 July 2018).

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**(7644):601–5.

Xia 2011
Xia Y, Luo H, Liu JP, Gluud C. Phyllanthus species for chronic hepatitis B virus infection. *Cochrane Database of Systematic Reviews* 2011, Issue 4. DOI: 10.1002/14651858.CD008960.pub2

Xia 2013
Xia Y, Luo H, Liu JP, Gluud C. Phyllanthus species versus antiviral drugs for chronic hepatitis B virus infection. *Cochrane Database of Systematic Reviews* 2013, Issue 4. DOI: 10.1002/14651858.CD009004.pub2

Xu 2010
Xu WS, Zhao KK, Miao XH, Ni W, Cai X, Zhang RQ, et al. Effect of oxymatrine on the replication cycle of hepatitis B virus in vitro. *World Journal of Gastroenterology* 2010;**16**(16):2028–37.

Yin 2011
Yin WH, Ni HH. Entecavir in combination with Kushensu for treating HBeAg positive chronic hepatitis B. *Clinical Rational Drug Use* 2011;**4**(34):60–1.

Zhang 2001
Zhang JP, Zhang M, Zhou JP, Liu FT, Zhou B, Xie WF, et al. Antifibrotic effects of matrine on in vitro and in vivo models of liver fibrosis in rats. *Acta Pharmacologica Sinica* 2001;**22**(2):183–6.

Zhang 2008
Zhang C, Nie HW, Cao XX. One case of fever induced by 0.6% oxymatrine salt water injection. *Clinical Journal of Medical Officer* 2008;**9**(4):635.

Zhang 2012a
Zhang CM. Combined application of oxymatrine and lamivudine in treating 62 cases of chronic hepatitis B. *Clinical Medical Engineering* 2012;**19**(6):935–6.

Zhang 2012b
Zhang YS. Lamivudine combined with Kushensu for chronic hepatitis B. *China Practical Medical* 2012;**7**(3):145–6.

Zhu 1998
Zhu YP. *Chinese Materia Medica-Chemistry, Pharmacology and Applications*. 1st Edition. Florida (USA): CRC Press, 1998.

Zhu 2009
Zhu ZC, Wang HZ, Yang F. Composite Sophorae injection in prevention of toxicity and adverse effects caused by chemotherapeutic agents. *Journal of Practical Oncology* 2009;**24**(6):592–4.

Zou 2003
Zou GZ, Li X, Ye J, Ye Y, Li HB. Effect of matrine injection combined with IFN on viral quantitative levels in the patients with chronic hepatitis B. *Anhui Medical and Pharmaceutical Journal* 2003;**7**(1):13–4.

Zou 2009
Zou YQ, Chen L, Yu CM. Preparation process of matrine and glucose injection. *China Pharmacist* 2009;**12**(12):1757–9.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Controlled Trials Register	Date will be given at review stage.	(sophor* or ku shen or kushen or matrine or oxymatrine or kujin) AND ((hepatitis B or hep B or hbv) and chronic)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	(sophor* or ku shen or kushen or matrine or oxymatrine or kujin) AND CENTRAL:TARGET MESH DESCRIPTOR Hepatitis B, Chronic EXPLODE ALL AND CENTRAL:TARGET ((hepatitis B or hep B or hbv) and chronic) AND CENTRAL:TARGET

(*Continued*)

		#2 OR #3 #1 AND #4
MEDLINE Ovid	1946 to the date of search	1. (sophor* or ku shen or kushen or matrine or oxymatrine or kujin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 2. exp Hepatitis B, Chronic/ 3. ((hepatitis B or hep B or hbv) and chronic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 4. 2 or 3 5. 1 and 4
Embase Ovid	1974 to the date of search	1. (sophor* or ku shen or kushen or matrine or oxymatrine or kujin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] 2. exp chronic hepatitis B/ 3. ((hepatitis B or hep B or hbv) and chronic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] 4. 2 or 3 5. 1 and 4
LILACS (Bireme)	1982 to the date of search	(sophor$ or ku shen or kushen or matrine or oxymatrine or kujin) [Words] and ((hepatitis B or hep B or hbv) and chronic) [Words]
Science Citation Index Expanded (Web of Science)	1900 to the date of search	#3 #2 AND #1 #2 TS=((hepatitis B or hep B or hbv) and chronic) #1 TS=(sophor* or ku shen or kushen or matrine or oxymatrine or kujin)
Conference Proceedings Citation Index - Science (Web of Science)	1990 to the date of search	#3 #2 AND #1 #2 TS=((hepatitis B or hep B or hbv) and chronic) #1 TS=(sophor* or ku shen or kushen or matrine or oxymatrine or kujin)
China Network Knowledge Infrastructure (CNKI)	1994 to the date of search	Search strategy in Chinese. #1 Title/Abstract=(matrine or oxymatrine or

(*Continued*)

		kushen or Radix sophorae flavescentis) #2 Title/Abstract=(chronic hepatitis B) #3 Text word=(random) #4 #1 AND #2 AND #3
Chongqing VIP (CQVIP)	1989 to the date of search	Search strategy in Chinese. #1 Title/Abstract=(matrine or oxymatrine or kushen or Radix sophorae flavescentis) #2 Title/Abstract=(chronic hepatitis B) #3 Text word=(random) #4 #1 AND #2 AND #3
Wanfang	1982 to the date of search	Search strategy in Chinese. #1 Title/Abstract=(matrine or oxymatrine or kushen or Radix sophorae flavescentis) #2 Title/Abstract=(chronic hepatitis B) #3 Text word=(random) #4 #1 AND #2 AND #3
SinoMed	1978 to the date of search	Search strategy in Chinese. #1 Title/Abstract=(matrine or oxymatrine or kushen or Radix sophorae flavescentis) #2 Title/Abstract=(chronic hepatitis B) #3 Text word=(random) #4 #1 AND #2 AND #3

CONTRIBUTIONS OF AUTHORS

NL: developed and drafted the protocol.

DZK: developed and co-ordinated the protocol.

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CG: developed, co-ordinated, and advised on the protocol.

JPL: initiated the review.

All authors commented and agreed to this final version of the protocol.

DECLARATIONS OF INTEREST

NL: none known.

DZK: none known.

DN: none known.

JCJ: none known.

CG: none known.

JPL: none known.

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NOTES

Cochrane Reviews can be expected to have a high percentage of overlap in the methods section because of standardised methods. In addition, overlap may be observed across several of our protocols as they share at least three common authors.