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[Intervention Review]

Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia

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ABSTRACT

Background

There are many pathological conditions leading to an elevated unconjugated bilirubin level (hyperbilirubinaemia) in neonates. Currently the standard therapies for unconjugated hyperbilirubinaemia include phototherapy and exchange transfusion. In addition to phototherapy, clofibrate has been studied as a treatment for hyperbilirubinaemia in several countries.

Objectives

To determine the efficacy and safety of clofibrate in combination with phototherapy versus phototherapy alone in unconjugated neonatal hyperbilirubinaemia.

Search methods

Randomised controlled trials were identified by searching MEDLINE (1950 to April 2012) before being translated for use in *The Cochrane Library*, EMBASE 1980 to April 2012 and CINAHL databases. All searches were re-run on 2 April 2012.

Selection criteria

We included trials where neonates with hyperbilirubinaemia received either clofibrate in combination with phototherapy or phototherapy alone or placebo in combination with phototherapy.

Data collection and analysis

Data were extracted and analysed independently by two review authors (MG and HM). Treatment effects on the following outcomes were determined: mean change in bilirubin levels, mean duration of treatment with phototherapy, number of exchange transfusions needed, adverse effects of clofibrate, bilirubin encephalopathy and neonatal mortality. Study authors were contacted for additional information. Studies were analysed for methodological quality in a 'Risk of bias' table.

Main results

Fifteen studies (two including preterm neonates and 13 including term neonates) were included in this review. All but one of the included studies were conducted in Iran. For preterm neonates, there was a significantly lower bilirubin level in the 100 mg/kg clofibrate group compared to the control group with a mean difference of -1.37 mg/dL (95% CI -2.19 mg/dL to -0.55 mg/dL) (-23 µmol/L; 95% CI -36 µmol/L to -9 µmol/L) after 48 hours. For the term neonates, there were significantly lower bilirubin levels in the clofibrate group compared to

the control group after both 24 and 48 hours of treatment with a weighted mean difference of -2.14 mg/dL (95% CI -2.53 mg/dL to -1.75 mg/dL) (-37 µmol/L; 95% CI -43 µmol/L to -30 µmol/L) and -1.82 mg/dL (95% CI -2.25 mg/dL to -1.38 mg/dL) (-31 µmol/L; 95% CI -38 µmol/L to -24 µmol/L), respectively.

There was a significantly lower duration of phototherapy in the clofibrate group compared to the control group for both preterm and term neonates with a weighted mean difference of -23.82 hours (95% CI -30.46 hours to -17.18 hours) and -25.40 hours (95% CI -28.94 hours to -21.86 hours), respectively.

None of the studies reported on bilirubin encephalopathy rates, neonatal mortality rates, or the levels of parental or staff satisfactions with the interventions.

Authors' conclusions

There are insufficient data from different countries on the use of clofibrate in combination with phototherapy for hyperbilirubinaemia to make recommendations for practice. Clofibrate has been withdrawn from the market in some countries and is no longer in use in adults (the primary indication) because of safety concerns. As such, we will no longer be updating this review.

PLAIN LANGUAGE SUMMARY

Clofibrate for neonatal jaundice

Jaundice is a common problem in the neonatal period typically in the first week of life. It is treated quite effectively using phototherapy whereby the baby is placed under special lights for up to three to four days. Clofibrate is used in some countries in combination with phototherapy to reduce the time the baby needs to spend under lights thereby reducing parental anxiety and improved parent-baby bonding opportunities.

We have reviewed the evidence using systematic literature searches and have synthesised outcome data to see if clofibrate does have an effect on time spent under lights. We identified 12 studies and the use of clofibrate reduced time spent under lights by an average of 23 hours for both term and preterm babies.

However, most of the studies were carried out in one country, Iran, so these findings may not be generalisable to other countries.

Clofibrate has been withdrawn from the market in some countries and is no longer in use in adults (the primary indication) because of safety concerns. As such, we will no longer be updating this review.

BACKGROUND

Description of the condition

Bilirubin is a naturally occurring antioxidant in the human body (Hammerman 1998); however, elevated levels of bilirubin, or 'hyperbilirubinaemia', is a neonatal complication that if treated promptly can usually be resolved in three to four days. This is a common problem in the neonatal period, occurring in around 60% of newborns (Maisels 1992). It is the most common cause of re-admissions to the hospital after early hospital discharge of term neonates (Escobar 2005). It is more common in preterm infants than in term infants, mainly because of a delay in the expression of hepatic glucuronyl transferase, the enzyme that conjugates bilirubin (Gartner 1994).

Bilirubin production and excretion follows a specific pathway. When the reticuloendothelial system breaks down old red blood cells, bilirubin is one of the waste products. This unconjugated bilirubin is in a lipid-soluble form that must be made water-soluble in order to be excreted. The unconjugated bilirubin is carried by albumin to the liver, where it is converted or conjugated and made water soluble. Once it is conjugated into a water-soluble form, bilirubin can be excreted in the urine.

There are many pathological conditions leading to an elevated unconjugated bilirubin level in neonates and these can be broadly grouped into haemolytic and non-haemolytic conditions. Under certain circumstances unconjugated bilirubin can be toxic to the central nervous system, resulting in encephalopathy and neurological impairment (Gourley 1997). Factors influencing bilirubin toxicity to the brain cells of newborn infants are complex and incompletely understood; they include those that affect the serum albumin concentration and those that affect the binding of bilirubin to albumin, the penetration of bilirubin into the brain, and the vulnerability of brain cells to the toxic effects of bilirubin. It is not known at what bilirubin concentration or under what circumstances significant risk of brain damage occurs or when the risk of damage exceeds the risk of treatment (AAP 1994).

Currently the standard therapies for hyperbilirubinaemia include phototherapy and exchange transfusion. These therapies aim to reduce high levels of unconjugated bilirubin or prevent the development of such high levels, and are usually instituted at different levels of bilirubin in different categories of infants, based on the recommendations of experts (AAP 1994; RCOG 2010).

Description of the intervention

Clofibrate is a fibric acid derivative used in the treatment of hyperlipoproteinaemia Type III and severe hypertriglyceridaemia. Clofibrate acts as an activator of peroxisome proliferator-activated receptors (PPARs), and thus it affects lipid metabolism. It acts to lower elevated serum lipids by reducing the very low-density lipoprotein fraction (S_f 20-400) rich in triglycerides. Serum cholesterol may be decreased, particularly in those patients whose cholesterol elevation is because of the presence of low-density lipoprotein as a result of Type III hyperlipoproteinaemia (DrugBank 2012).

It has been studied as a treatment for hyperbilirubinaemia in France, Iran, Mexico and Spain. It has been used to prevent the need for phototherapy and as an adjunct to phototherapy. It is usually

given as a syrup or in liquid form via orogastric tube. The dosage commonly used for neonates is 100 mg/kg given in a single dose and its safety profile at this dosage has been examined (Bourget 1995). In adults (500 mg every six to 12 hours) its adverse effects include nausea and pruritus. No adverse effects have been noted in trials on neonates but, to date, no long-term follow-up has been carried out.

How the intervention might work

Phototherapy is the first-line treatment for neonatal hyperbilirubinaemia and reduces serum bilirubin levels by converting bilirubin into a water-soluble, more easily excretable form. This molecular conversion occurs when bilirubin accumulating in the skin of jaundiced infants is exposed to light of wavelengths 425 nm to 475 nm (blue-green spectrum) (Tan 1982). Phototherapy devices emit special light within this range and this is often referred to as 'special' lights. Clofibrate potentially aids this by increasing bilirubin conjugation and excretion via induction of glucuronyl transferase activity (Bourget 1995). Glucuronyl transferase is a liver enzyme that changes bilirubin into a water-soluble form that can be excreted in the bile. In Gilbert's syndrome, clofibrate decreases serum total bilirubin concentrations by increasing the glucuronidation of bilirubin, thus promoting the overall hepatic transport of bilirubin (Kutz 1984).

Why it is important to do this review

One review of English-language papers on the effectiveness of clofibrate in combination with phototherapy for neonatal hyperbilirubinaemia recommended that research be carried out into the effectiveness of clofibrate for unconjugated hyperbilirubinaemia (RCOG 2010). This review indicates that clofibrate could potentially result in a clinically significant reduction in the duration of phototherapy. If this is demonstrated in the current review, this would have huge potential in terms of healthcare costs owing to reduced stays in paediatric units or neonatal intensive care units. It would also be important for neonates and their parents or carers by reducing separation and associated anxiety and increasing bonding opportunities in the neonatal period. To this end a review of all studies, not just English-language papers, of clofibrate in combination with phototherapy in neonatal hyperbilirubinaemia is warranted.

Editor's note: Clofibrate has been withdrawn from the market in some countries and is no longer in use in adults (the primary indication) because of safety concerns (Oliver 1984). As such, we will no longer be updating this review.

OBJECTIVES

In patients with unconjugated hyperbilirubinaemia requiring treatment:

1. to determine the effects of clofibrate in combination with phototherapy versus phototherapy alone on:
 - a. bilirubin levels (specifically bilirubin levels after initiation of phototherapy);
 - b. duration of phototherapy;
 - c. frequency of exchange transfusion;
 - d. incidence of bilirubin encephalopathy and long-term neurodevelopmental impairment associated with unconjugated hyperbilirubinaemia;

2. to determine the frequency and nature of side effects of clofibrate when used to treat unconjugated hyperbilirubinaemia in neonates.

We intended to perform the following subgroup analyses:

1. preterm (less than 37 completed weeks of gestation) and term (37 weeks or more of gestation) neonates;
2. haemolytic versus non-haemolytic causes of hyperbilirubinaemia;
3. studies that used different dosages of clofibrate;
4. studies that used phototherapy at serum bilirubin levels less than 255 µmol/L.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised and quasi-randomised controlled trials. We included only studies with individual participant allocation and did not include cross-over studies. We excluded studies of prophylactic phototherapy.

Types of participants

We included studies of term and preterm neonates with unconjugated hyperbilirubinaemia requiring phototherapy as defined by the author.

Types of interventions

We included studies in which participants received clofibrate (of any dosage) in combination with phototherapy in the treatment arm(s), and received either phototherapy alone or placebo clofibrate in combination with phototherapy in the comparison arm(s).

We did not include studies where phototherapy was given after relapse of hyperbilirubinaemia following successful phototherapy (rebound jaundice).

Types of outcome measures

Primary outcomes

1. Mean change in bilirubin levels (mg/dL or µmol/L) over 24 hours, 48 hours, 72 hours.
2. Mean duration of treatment with phototherapy (hours).
3. Number of exchange transfusions needed.
4. Any adverse effects of clofibrate.
5. Bilirubin encephalopathy.
6. Neonatal mortality.

Secondary outcomes

1. Parental anxiety.
2. Clinical staff satisfaction with treatment.

Search methods for identification of studies

Electronic searches

We developed a search strategy designed to capture all systematic reviews, and randomised or quasi-randomised controlled clinical

trials assessing the effectiveness of clofibrate to treat jaundice in neonates.

The population stem of the search strategy consisted of both subject descriptors and text words describing newborn infants with high levels of bilirubin, those diagnosed with jaundice or the associated complications of encephalopathy or kernicterus. Likewise, we searched for the intervention clofibrate as a subject heading where available and as a text word ([Appendix 1](#)).

We developed the search initially in the MEDLINE database ([Appendix 1](#)) and then ran across all years to the present (1950 to April 2012) before being translated for use in *The Cochrane Library* ([Appendix 2](#)), EMBASE (1980 to April 2012) ([Appendix 3](#)) and CINAHL ([Appendix 4](#)) databases. Since we were unable to identify a validated methodology filter for retrieving systematic reviews and controlled clinical trials in the CINAHL database, we planned to run only the population and intervention parts of the strategy.

We ran searches in the MEDLINE In-Process database ([Appendix 5](#)) and in CENTRAL to capture the latest studies.

Clinical trials registries

We searched the following clinical trials registries on 2 April 2012 using terms 'clofibrate' and 'atromid':

- www.clinicaltrials.gov;
- www.irct.ir/index.php;
- www.controlled-trials.com/mrct.

Searching other resources

We did not conduct any handsearching of journals or conference proceedings for this review.

We checked the reference list of all included studies and of systematic reviews on this topic.

We carried out an internet search using both Google and Google Scholar. Last checked on 2 April 2012.

Data collection and analysis

Selection of studies

Two reviewer authors (HM and MG) reviewed all citations and abstracts. A third review author (JR) was available to resolve any disagreement by discussion or adjudication, or both, was not needed. We obtained full-text papers, and then two review authors (HM and MG) selected those that met the inclusion criteria and again a third review author (JR) was available to resolve any disagreement by discussion or adjudication, or both.

Data extraction and management

Two review authors (HM and MG) extracted data independently using standardised data extraction sheets (e.g. [Appendix 6](#)) and both entered the data into Review Manager (RevMan) 5.1 ([RevMan 5.1](#)).

Assessment of risk of bias in included studies

The review authors based their criteria for quality assessment on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). We assessed the bias and

complete the 'Risk of bias' table. We were interested in the following types of bias:

Selection bias

1. Sequence generation (Did the study generate the allocation sequence adequately?) For each included study, we categorised the method used to generate the allocation sequence as:
 - a. low risk (any truly random process, e.g. random number table; computer random number generator);
 - b. high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
 - c. unclear.
2. Allocation concealment (Did the study conceal the allocation adequately?) For each included study, we categorised the method used to conceal the allocation sequence as:
 - a. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
 - b. high risk (open random allocation; unsealed or non-opaque envelopes, alternation, date of birth);
 - c. unclear.

Performance bias

1. Blinding (Did the authors conceal knowledge of the allocated intervention adequately during the study? At study entry? At the time of outcome assessment?) For each included study, we categorised the methods used to blind study personnel from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes. We categorised the methods as:
 - a. low risk, high risk or unclear for participants;
 - b. low risk, high risk or unclear for personnel;
 - c. low risk, high risk or unclear for outcome assessors.

Attrition bias

1. Incomplete outcome data (Did the study address incomplete outcome data adequately?) For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether the study reported attrition and exclusions, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion (where reported), and whether the authors balanced missing data across groups or related to outcomes. Where the trial authors reported or supplied sufficient information, we re-included missing data in the analyses. We categorised the methods as:
 - a. low risk (less than 20% missing data);
 - b. high risk (20% or more missing data);
 - c. unclear risk.

Selective reporting bias

1. Incomplete reporting (Are reports of the study free of suggestion of selective outcome reporting?) For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:
 - a. low risk (where it is clear that the trial authors have reported all of the study's pre-specified outcomes and all expected outcomes of interest to the review);

- b. high risk (where the trial's authors have not reported all the study's pre-specified outcomes; they did not pre-specify one or more reported primary outcomes; they reported outcomes of interest incompletely so that they cannot be used; study failed to include results of a key outcome that the authors should have reported);
- c. unclear risk.

Other sources of bias

1. Other sources of bias (Was the study apparently free of other problems that could put it at a high risk of bias?) For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early owing to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:
 - a. yes;
 - b. no;
 - c. unclear.

We planned to explore the impact of the level of bias through undertaking sensitivity analyses if needed.

Measures of treatment effect

We originally planned to use weighted mean difference (WMD) when analysing continuous data and risk ratio (RR) when analysing dichotomous data. However, based on the advice in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) we opted to use mean endpoint scores instead of mean change from baseline.

We also planned to calculate the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for significant risks, but as no adverse effects were reported we did not do this.

Unit of analysis issues

We planned to combine data from the treatment arms of studies with multiple treatment arms and compare them with placebo but made a post-hoc decision to report as separate comparisons based on dosage of clofibrate used.

Dealing with missing data

In cases where adequate information was not available within the papers, we contacted the investigators and asked them to supply additional information using a standardised form. Where the investigators provided no further usable data, we imputed missing data using formulae from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We carried out sensitivity analyses to examine the effect of including these studies.

If bilirubin levels were reported as milligrams per decilitre (mg/dL), we used these data in the meta-analyses and added conversion to micromoles per litre (μmol/L) by multiplying by a factor of 17.1 (JAMA 2001) in brackets.

Assessment of heterogeneity

We assessed heterogeneity between studies using the I^2 statistic and by visual inspection of the results. We stated that if

heterogeneity was present then we would re-examine the studies to see if there was a clinical explanation for it. We used $I^2 > 50\%$ to be indicative of moderate heterogeneity (Higgins 2003).

Assessment of reporting biases

We performed a funnel plot analysis to check for small study effects, including publication bias (see Figure 1).

Figure 1. Funnel plot of comparison: 1 Phototherapy + clofibrate 100 mg/kg versus phototherapy alone, outcome: 1.2 Mean total serum bilirubin ($\mu\text{mol/L}$) after 48 hours.

Data synthesis

For dichotomous outcomes, we calculated RR and their 95% confidence intervals (CIs). We used a fixed-effect model for analyses as recommended by the Cochrane Neonatal Group (Cochrane Neonatal Review Group 2011).

For continuous outcomes, we had planned to calculate the mean difference (MD) of change from baseline to end point using a fixed-effect model but we made a post-hoc decision to use end point scores based on advice in Cochrane handbook (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

While we accept that we should perform and interpret subgroup analyses with caution because multiple analyses can lead to false-positive conclusions (Davey Smith 2008), we carried out the intended subgroup analyses as follows:

1. preterm (less than 37 completed weeks of gestation) and term (37 weeks or more of gestation) neonates;
2. studies that used different dosages (100 mg/kg and greater versus less than 100 mg/kg);

3. studies that used phototherapy at serum bilirubin levels less than 255 $\mu\text{mol/L}$.

We did not find any studies that examined haemolytic hyperbilirubinaemia.

Sensitivity analysis

Planned sensitivity analysis: we did not use imputed data so we did not carry out this planned sensitivity analysis.

RESULTS

Description of studies

Results of the search

Nineteen published studies were identified. Twelve studies met the inclusion criteria. Seven trials were excluded. A total of 739 neonates were included in these studies (range 40 to 90 neonates per study). The details of each of these studies are given in the [Characteristics of included studies](#) table.

Included studies

All studies were single-centre studies and all except one were carried out in Iran. Neonates in one study received phototherapy at home while in the other 11 studies phototherapy was given in the hospital. Clofibrate was mostly given orally in a single dose and in two studies enteral water was given as placebo to the control group.

Nearly all of the studies used bilirubin level, duration of phototherapy, adverse effects and number of exchange transfusions as outcomes while parental or healthcare professional satisfaction was not reported in any study.

Subgroup analyses

One study was quasi-randomised ([Badeli 2008](#)) and sensitivity analysis was performed after excluding this study instead of the planned subgroup analysis.

Two studies ([Mohammadzadeh 2009](#); [Sakha 2009](#)) exclusively included preterm infants and were analysed separately from the other 10 studies ([Caballero-Nogu 2001](#); [Mohammadzadeh 2005](#); [Eghbalian 2007](#); [Moslehi 2007](#); [Zahedpasha 2007](#); [Badeli 2008](#); [Zahedpasha 2008](#); [Ghotbi 2009](#); [Sharafi 2010](#); [Eyvazzadeh 2011](#)) including term neonates.

We did not identify any studies that included neonates with haemolytic hyperbilirubinaemia so this a priori subgroup analysis was not carried out.

One study ([Sharafi 2010](#)) specified a minimum entry level of 239 $\mu\text{mol/L}$ and one study ([Sakha 2009](#)) did not report on minimum bilirubin entry levels. In both studies the mean baseline bilirubin levels were greater than 291 $\mu\text{mol/L}$ so the planned subgroup analysis of studies using phototherapy at serum bilirubin levels less than 255 $\mu\text{mol/L}$ was not carried out. .

Excluded studies

Four of the studies were excluded because they examined clofibrate as prophylactic intervention for neonatal jaundice/hyperbilirubinaemia. The fifth study was a case-control study. The sixth and seventh studies were excluded because there was no placebo-control group in one study and the population in other study consisted only of neonates with prolonged jaundice (> 14 days).

Risk of bias in included studies

See [Figure 2](#) for full 'Risk of bias' table.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Alipour 2011	⊖	?	?	?	?
Badeli 2008	⊖	⊖	⊕	⊖	⊖
Caballero-Noguéz 2001	⊕	?	⊕	⊖	⊖
Eghbalian 2007	⊕	⊖	⊕	⊖	⊖
Eyvazzadeh 2011	⊖	⊖	⊕	⊖	⊖
Fallah 2012	⊕	⊕	⊕	⊖	⊕
Ghotbi 2009	⊖	?	⊕	?	?
Habibi 2012	⊕	?	⊕	?	?
Mohammadzadeh 2005	⊕	⊖	⊕	⊖	⊖
Mohammadzadeh 2009	⊖	⊕	⊕	⊕	⊕
Moslehi 2007	⊕	⊖	⊕	⊖	⊖
Sakha 2009	⊕	⊕	⊕	⊕	⊕
Sharafi 2010	⊖	⊖	⊕	⊖	⊖
Zahedpasha 2007	⊖	⊖	⊕	⊖	⊖
Zahedpasha 2008	⊖	⊖	⊕	⊖	⊖

Allocation

Three of the studies (Badeli 2008; Ghotbi 2009; Eyvazzadeh 2011) allocated neonates alternately to the treatment groups and so were considered to be quasi-randomised studies. The remaining studies used either random-numbers tables (Caballero-Noguz 2001; Mohammadzadeh 2005; Eghbalian 2007; Moslehi 2007; Sakha 2009) or did not state how the randomisation was carried out (Zahedpasha 2007; Zahedpasha 2008; Mohammadzadeh 2009; Sharafi 2010).

Blinding

One of the studies (Mohammadzadeh 2009) was double-blinded and the remainder did not report on blinding of patient, outcome assessor or clinical staff.

Incomplete outcome data

In the nine studies that used random allocation of interventions, no neonates were excluded after randomisation, so there were no missing data in any of these studies.

Selective reporting

One study (Eghbalian 2007) claimed that all infants were examined at the second day after discharge for any probable pharmacological side effect, but the outcome of this assessment was not reported in the results section.

Other potential sources of bias

No other potential sources of bias were identified.

Serum bilirubin was assessed in all included studies. The blood test was performed before treatment and repeated 12 hours after treatment and then daily until phototherapy was discontinued. It is not clear who performed the blood test in the all included studies.

Effects of interventions

Phototherapy plus clofibrate 100 mg/kg versus phototherapy or phototherapy plus placebo group (Comparison 1)

Ten studies were included in this comparison. Two studies (Mohammadzadeh 2009; Sakha 2009) included preterm neonates and the remaining eight studies (Mohammadzadeh 2005; Eghbalian 2007; Zahedpasha 2007; Badeli 2008; Zahedpasha 2008; Ghotbi 2009; Eyvazzadeh 2011; Habibi 2012) included term neonates.

Mean total serum bilirubin 24 hours after initiation of treatment (Outcome 1.1)

Preterm neonates

Two studies (Mohammadzadeh 2009; Sakha 2009) contributed to this analysis. There was no significant difference between the treatment groups for the preterm neonates after 24 hours of treatment (WMD 0.55 mg/dL; 95% CI -0.48 mg/dL to 1.58 mg/dL [9 μ mol/L; 95% CI -8 μ mol/L to 27 μ mol/L]) (Analysis 1.1). Heterogeneity was high ($I^2 = 72\%$).

Term neonates

Eight studies (Mohammadzadeh 2005; Eghbalian 2007; Zahedpasha 2007; Badeli 2008; Zahedpasha 2008; Ghotbi 2009; Eyvazzadeh 2011; Habibi 2012) contributed to this analysis. There was a significantly lower bilirubin level in the phototherapy plus

clofibrate group compared to the phototherapy alone or plus placebo group (WMD -2.14 mg/dL; 95% CI -2.53 mg/dL to -1.75 mg/dL [-37 μ mol/L; 95% CI -43 μ mol/L to -30 μ mol/L]) (Analysis 1.1). Heterogeneity was high ($I^2 = 71\%$). After the quasi-randomised studies (Badeli 2008; Ghotbi 2009; Eyvazzadeh 2011) were excluded from the analysis the MD was -1.67 mg/dL (95% CI -2.27 mg/dL to -1.08 mg/dL [-29 μ mol/L; 95% CI -39 μ mol/L to -18 μ mol/L]). Heterogeneity was high ($I^2 = 72\%$).

Mean total serum bilirubin 48 hours after initiation of treatment (Outcome 1.2)

Preterm neonates

Two studies (Mohammadzadeh 2009; Sakha 2009) contributed to this analysis. There was a significantly lower bilirubin level in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -1.37 mg/dL; 95% CI -2.19 mg/dL to -0.55 mg/dL [-23 μ mol/L; 95% CI -37 μ mol/L to -9 μ mol/L]) (Analysis 1.2). Heterogeneity was high ($I^2 = 94\%$).

Term neonates

Six studies (Mohammadzadeh 2005; Eghbalian 2007; Zahedpasha 2007; Zahedpasha 2008; Ghotbi 2009; Eyvazzadeh 2011) contributed to this analysis. There was a significantly lower bilirubin level in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -1.82 mg/dL; 95% CI -2.25 mg/dL to -1.38 mg/dL [-31 μ mol/L; 95% CI -38 μ mol/L to -24 μ mol/L]) (Analysis 1.2). Heterogeneity was low ($I^2 = 18\%$). After the quasi-randomised studies (Eyvazzadeh 2011; Ghotbi 2009) were excluded from the analysis the MD was -1.70 mg/dL; 95% CI -2.29 mg/dL to -1.10 mg/dL [-29 μ mol/L; 95% CI -39 μ mol/L to -19 μ mol/L]). Heterogeneity was low ($I^2 = 42\%$).

Mean duration of phototherapy (hours) (Outcome 1.3)

Preterm neonates

Two studies (Mohammadzadeh 2009; Sakha 2009) contributed to this analysis. There was a significantly lower duration of phototherapy in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -23.82 hours; 95% CI -30.46 hours to -17.18 hours) (Analysis 1.3). There was no heterogeneity ($I^2 = 0\%$).

Term neonates

Four studies (Alipour 2011; Badeli 2008; Eghbalian 2007; Mohammadzadeh 2005) contributed to this analysis. There was a significantly lower duration of phototherapy in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -25.40 hours; 95% CI -28.94 hours to -21.86 hours) (Analysis 1.3). Heterogeneity was high ($I^2 = 64\%$). After the quasi-randomised studies (Alipour 2011; Ghotbi 2009) were excluded from the analysis the WMD was -20.22 hours (95% CI -26.39 hours to -14.03 hours). Heterogeneity was moderate ($I^2 = 48\%$).

Number of exchange transfusions needed (Outcome 1.4)

Five studies (Caballero-Noguz 2001; Eghbalian 2007; Eyvazzadeh 2011; Mohammadzadeh 2005; Mohammadzadeh 2009) reported on this outcome and no exchange transfusions were required in four of the studies. In one study (Mohammadzadeh 2009) two

neonates needed an exchange transfusion during treatment, one in the clofibrate group and the other in the placebo group.

Adverse effects of clofibrate (Outcome 1.5)

Eight studies (Caballero-Noguz 2001; Mohammadzadeh 2005; Eghbalian 2007; Badeli 2008; Zahedpasha 2008; Ghotbi 2009; Mohammadzadeh 2009; Eyvazzadeh 2011) reported on this outcome and no adverse effects were reported. There are no summary statistics so subgroup analyses for this outcome.

None of the studies reported the mean total serum bilirubin after 72 hours after initiation of treatment, bilirubin encephalopathy, neonatal mortality, parental anxiety and clinical staff satisfaction with treatment.

Phototherapy plus clofibrate 50 mg/kg versus phototherapy alone or plus placebo (Comparison 2)

Mean total serum bilirubin 24 hours after initiation of treatment (Outcome 2.1)

Preterm neonates

None of the studies reported the mean total serum bilirubin levels after 24 hours in preterm neonates.

Term neonates

Three studies (Moslehi 2007; Sharafi 2010; Fallah 2012) contributed to this analysis. There was a significantly lower bilirubin level in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -3.70; 95% CI -4.11 mg/dL to -3.30 mg/dL [-63 µmol/L; 95% CI -70 µmol/L to -56 µmol/L]) (Analysis 2.1). Heterogeneity was high ($I^2 = 95\%$).

Mean total serum bilirubin 48 hours after initiation of treatment (Outcome 2.2)

Preterm neonates

None of the studies reported the mean total serum bilirubin levels after 48 hours in preterm neonates.

Term neonates

Two studies (Sharafi 2010; Fallah 2012) contributed to this analysis. There was a significantly lower bilirubin level in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -3.41 mg/dL; 95% CI -3.91 mg/dL to -2.91 mg/dL [-58 µmol/L; 95% CI -67 µmol/L to -50 µmol/L]) (Analysis 2.2). Heterogeneity was high ($I^2 = 85\%$).

Mean duration of phototherapy (hours) (Outcome 2.3)

Preterm neonates

None of the studies reported the mean duration of phototherapy in preterm neonates.

Term neonates

Two studies (Fallah 2012; Moslehi 2007) contributed to this analysis. There was a significantly shorter duration of phototherapy in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -10.85 hours; 95% CI -12.48 hours to -9.23 hours) (Analysis 2.3). Heterogeneity was moderate ($I^2 = 47\%$).

Number of exchange transfusions needed (Outcome 2.4)

Preterm neonates

None of the studies reported the number of exchange transfusions in preterm neonates.

Term neonates

One study (Fallah 2012) contributed to this analysis. There was a single exchange transfusion in the control group. Heterogeneity was not applicable.

Adverse effects of clofibrate (Outcome 2.4)

Three studies (Moslehi 2007; Sharafi 2010; Fallah 2012) reported on this outcome and two adverse effects of clofibrate were report. No summary statistics were available.

None of the studies reported mean total serum bilirubin after 72 hours of treatment, bilirubin encephalopathy, neonatal mortality, parental anxiety and clinical staff satisfaction with treatment.

Phototherapy plus clofibrate 25 mg/kg versus phototherapy alone or plus placebo (Comparison 3)

One study (Moslehi 2007) contributed to this analysis.

Mean total serum bilirubin 24 hours after initiation of treatment (Outcome 3.1)

Preterm neonates

No studies were identified for mean total serum bilirubin levels after 24 hours in preterm neonates.

Term neonates

One study (Moslehi 2007) contributed to this analysis. There was a significantly lower bilirubin level in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -4.70 mg/dL; 95% CI -5.25 mg/dL to -4.15 mg/dL [-80 µmol/L; 95% CI -90 µmol/L to -71 µmol/L]) (Analysis 3.1). Heterogeneity was not applicable.

Mean duration of phototherapy (hours) (Outcome 3.2)

Preterm neonates

No studies were identified for this subgroup

Term neonates

One study (Moslehi 2007) contributed to this analysis. There was a significantly shorter duration of phototherapy in the phototherapy plus clofibrate group compared to the phototherapy alone or plus placebo group (WMD -11.10 hours; 95% CI -12.73 hours to -9.47 hours) (Analysis 3.2). Heterogeneity was not applicable.

Adverse effects of clofibrate (Outcome 3.3)

One study (Moslehi 2007) reported on this outcome and no exchange transfusions were required. There were no summary statistics for this outcome.

None of the studies reported the mean total serum bilirubin after 48 and 72 hours of treatment, bilirubin encephalopathy, neonatal mortality, parental anxiety and clinical staff satisfaction with treatment.

DISCUSSION

Summary of main results

Seven studies (Mohammadzadeh 2005; Eghbalian 2007; Zahedpasha 2007; Badeli 2008; Zahedpasha 2008; Ghotbi 2009; Eyvazzadeh 2011) reported that clofibrate in combination with phototherapy was more effective than phototherapy alone in term neonates at reducing bilirubin levels 24 and 48 hours after start of phototherapy. Two studies (Mohammadzadeh 2009; Sakha 2009) reported that the addition of clofibrate to phototherapy did not improve the effectiveness of phototherapy in preterm neonates. No adverse effects were reported in any of the studies. There were no reported exchange transfusions in the majority of studies. One study (Mohammadzadeh 2009) reported that two neonates needed an exchange transfusions during treatment; one in the clofibrate plus phototherapy group and the other in the phototherapy only group. None of the studies reported on bilirubin encephalopathy rates, neonatal mortality rates, or the levels of parental or staff satisfactions with the interventions.

Overall completeness and applicability of evidence

The objective of this review was to compare the effectiveness of clofibrate in combination with phototherapy for the treatment of neonatal hyperbilirubinaemia. All nine included studies reported on at least one of the four primary outcomes but none report on the remaining outcomes. We believe this review provides a relevant answer to the question of effectiveness of clofibrate in combination with phototherapy, but the evidence is susceptible to bias. In particular, there was no evidence on severe outcomes such as bilirubin encephalopathy or neonatal mortality. Trial settings, care providers and the study populations were comparable in the studies and the findings of these trials are generalisable. However, our planned subgroup analyses by bilirubin less than 255 µmol/L or by haemolytic hyperbilirubinaemia were not possible.

Quality of the evidence

The quality of evidence was low to moderate in all but one of the studies, with high risk of bias resulting from a lack of blinding.

Potential biases in the review process

Although our search was extensive, we cannot exclude the possibility that we have missed relevant evidence. We tried to contact the authors of the original studies but no responses were received. Our search of grey literature, the pursuit of trials listed in clinical trial registers and the fact that we applied no restrictions based on language or publication status aimed to avoid publication bias, location bias, citation bias, language bias and outcome reporting bias. Multiple publication bias did not occur but there

was one case of duplicate publication that resulted in the journal withdrawing the published article.

Agreements and disagreements with other studies or reviews

We found no other systematic reviews examining the use of clofibrate in combination with phototherapy to treat neonatal hyperbilirubinaemia.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence that clofibrate in combination with phototherapy has a beneficial effect on the duration of phototherapy needed for neonates with hyperbilirubinaemia. However, it is unclear if these results, mainly from studies in a single country, are generalisable to other countries. The rates of exchange transfusion were quite low with only three neonates requiring an exchange transfusion in all the studies, which is to be expected with the effectiveness of phototherapy. As the indications for exchange transfusions may differ from country to country, we would need to replicate these findings in other countries before a conclusion could be made for this outcome. Adverse effect data from the randomised controlled trials of clofibrate are limited, and no definite recommendations based on available data can be made. Similarly no cases of either bilirubin encephalopathy or neonatal mortality were reported in any study so no definite recommendations for these outcomes can be made.

Implications for research

It is important that clofibrate in combination with phototherapy be examined in other countries before it can be assessed as effective and safe for use in all countries. Any such study should include outcome measures other than need for or duration of phototherapy and serum bilirubin levels, such as length of hospital stay, re-admission with jaundice and perhaps health economics analysis.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Alipour 2011

Methods	Design: CCT Blinding: not reported Randomisation: alternation Follow-up: not reported <u>Inclusion criteria</u> Term neonates with hyperbilirubinaemia <u>Exclusion criteria</u> Congenital anomalies Haemolytic disease Dehydration Infection G6PD deficiency
Participants	<u>Phototherapy plus clofibrate group</u> Gender: male 29, female 11 Mean age at baseline: 6 ± 2 days Mean bilirubin at baseline: not reported Mean GA at birth: not reported Mean birthweight: 3260 ± 400 g <u>Phototherapy group</u> Gender: male 21, female 11 Mean age at baseline: 5 ± 2 days Mean bilirubin at baseline: not reported Mean GA at birth: not reported Mean birthweight: 3231 ± 370 g
Interventions	<u>Phototherapy plus clofibrate group</u> 4 (250 W) lamps positioned 30 cm above the baby + single dose of 100 mg/kg clofibrate <u>Phototherapy group</u> 4 (250 W) lamps positioned 30 cm above the baby
Outcomes	Bilirubin levels Adverse effects
Notes	-

Risk of bias
Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia (Review)

Alipour 2011 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Infants were randomly divided by two groups ... by alternate time of admission"
Allocation concealment (selection bias)	Unclear risk	No statement on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear on outcomes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No statement on blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding

Badeli 2008

Methods	Design: CCT Blinding: not reported Randomisation: alternation Follow-up: 1 month <u>Inclusion criteria</u> All selected neonates were born at term (with GA of 38 to 41 weeks), breastfed, had TSB levels between 15 mg/dL and 29.9 mg/dL and body weight 2500 g and 4000 g <u>Exclusion criteria</u> Dehydration Infection ABO or Rh incompatibility G6PD deficiency Conjugated bilirubin above 2 mg/dL or exceeding 15% of TSB Congenital anomalies
Participants	<u>Phototherapy plus clofibrate group</u> Gender: 26 male, 19 female Mean age at baseline: 120 ± 36 hours Mean bilirubin at baseline: 18.4 ± 1.4 mg/dL Mean GA at birth: not reported Mean birthweight: 3190 ± 268 g <u>Phototherapy group</u> Gender: 24 male, 21 female Mean age at baseline: 134 ± 50 hours Mean bilirubin at baseline: 18.4 ± 1.8 mg/dL Mean GA at birth: not reported Mean birthweight: 3151 ± 289 g
Interventions	<u>Phototherapy plus clofibrate group</u> 4 special white 420 to 480 nm lamps being used less than 240 hours and adjusted to about 30 cm above neonate + single dose of 100 mg/kg clofibrate

Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia (Review)

Badeli 2008 (Continued)

Phototherapy group
4 special white 420 to 480 nm lamps being used less than 240 hours and adjusted to about 30 cm above neonate

Outcomes	TSB and indirect bilirubin were measured every 12 hours till the end of phototherapy
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Were randomly allocated to clofibrate group (G1) and control group (G2) alternately; i.e. the first patient to group G1, the second one to G2, and so on"
Allocation concealment (selection bias)	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Caballero-Noguéz 2001

Methods	Design: RCT Blinding: not reported Randomisation: random numbers Follow-up: not reported <u>Inclusion criteria</u> All selected neonates were born more than 28 weeks GA with an 1-minute Apgar 7 or greater <u>Exclusion criteria</u> Digestive tract problems Blood group incompatibility (ABO or Rh) Obstetric trauma Sepsis Congenital malformations Diabetic mother Erythrocyte changes Polycythaemia
Participants	<u>Phototherapy plus clofibrate group</u> Gender: 8 male, 4 female Mean age at baseline: 113 ± 46 hours Mean bilirubin at baseline: 18.6 ± 3.7 mg/dL Mean GA at birth: 35.5 ± 3.1 weeks Mean birthweight: 2341 ± 0.69 g

Caballero-Noguéz 2001 (Continued)

Phototherapy group
Gender: 7 male, 2 female
Mean age at baseline: 101 ± 41 hours
Mean bilirubin at baseline: 16.6 ± 4.1 mg/dL
Mean GA at birth: 36.0 ± 2.1 weeks
Mean birthweight: 2454 ± 0.66 grams

Interventions	<u>Phototherapy plus clofibrate group</u> 6 fluorescent white lamps positions 50 cm above neonate + single oral dose of 100 mg/kg clofibrate <u>Phototherapy group</u> 6 fluorescent white lamps positioned 50 cm above neonate
Outcomes	TSB Indirect bilirubin
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"números aleatorios" (random numbers)
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Eghbalian 2007

Methods	Design: RCT Blinding: not reported Randomisation: random numbers table Follow-up: 2 days <u>Inclusion criteria</u> All selected neonates were born at health breastfed term with TSB levels between 15 and 25 mg/dL and body weight above 2500 g <u>Exclusion criteria</u> Dehydration Signs of sepsis Haemolytic diseases (ABO or Rh incompatibility) Congenital anomalies
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Eghbalian 2007 (Continued)

Requiring an exchange transfusion

Participants	<p><u>Phototherapy plus clofibrate group</u> Gender: 15 male, 15 female Mean age at baseline: not reported Mean bilirubin at baseline: 20.8 ± 2.9 mg/dL Mean GA at birth: not reported Mean birthweight: not reported</p> <p><u>Phototherapy group</u> Gender: 21 male, 9 female Mean age at baseline: not reported Mean bilirubin at baseline: 20.9 ± 4.3 mg/dL Mean GA at birth: not reported Mean birthweight: not reported</p>
Interventions	<p><u>Phototherapy plus clofibrate group</u> 8 blue lamps (wavelength 420 to 450 nm) 25 cm above the cot + a single 100 mg/kg oral dose of clofibrate</p> <p><u>Phototherapy group</u> 8 blue lamps (wavelength 420 to 450 nm) 25 cm above the cot</p>
Outcomes	<p>Bilirubin levels Duration of phototherapy Number of exchange transfusions needed Adverse effects of clofibrate Rebound jaundice</p>
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a table of random numbers"
Allocation concealment (selection bias)	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Eyvazzadeh 2011

Methods	Design: CCT
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Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia (Review)

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Eyvazzadeh 2011 (Continued)

Blinding: not reported
Randomisation: alternation
Follow-up: 1 month

Inclusion criteria

Term neonates with jaundice

Exclusion criteria

Congenital anomalies

Haemolytic disease

Dehydration

Infection

G6PD deficiency

Participants
Phototherapy plus clofibrate group

Gender: Not reported on per group basis - overall 31 were male and 29 female

Mean age at baseline: not reported

Mean bilirubin at baseline: 17.22 ± 3.03 mg/dL

Mean GA at birth: not reported

Mean birthweight: not reported

Phototherapy group

Mean age at baseline: not reported

Mean bilirubin at baseline: 17.86 ± 3.04 mg/dL

Mean GA at birth: not reported

Mean birthweight: not reported

Interventions
Phototherapy plus clofibrate group

Phototherapy methods not specified + single dose of 100 mg/kg clofibrate

Phototherapy group

Phototherapy methods not specified

Outcomes

TSB

Notes

-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Infants were randomly divided by two group...by a alternate allocation method"
Allocation concealment (selection bias)	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias)	High risk	Not reported

Eyvazzadeh 2011 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
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Fallah 2012

Methods	Design: RCT Blinding: single blind Randomisation: computerised randomisation Follow-up: not stated
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Inclusion criteria:
Body weight: 2500 to 4000 g
GA: 38 to 42 weeks
Breastfed
TSB: 17 to 29.9 mg/dL
Normal vaginal delivery

Exclusion criteria:
Sepsis
Anaemia
Severe asphyxia
Haemolytic diseases
Indirect hyperbilirubinaemia
Major congenital anomalies
Underlying hepatic disorders

Participants	<u>Phototherapy plus clofibrate group</u> Gender: 16 male, 14 female Mean bilirubin at baseline: 19.54 ± 3.07 mg/dL Mean GA at birth: 38.23 ± 0.971 weeks Mean birthweight: 3202 ± 370 g <u>Phototherapy group</u> Gender: 14 male, 16 female Mean age at baseline: 4.97 ± 2.16 days Mean bilirubin at baseline: 19.5 ± 2.21 mg/dL Mean GA at birth: 37.87 ± 1.07 weeks Mean birthweight: 3193.67 ± 369 g
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Interventions	<u>Phototherapy plus clofibrate group</u> 4 special blue lamps (Phillips) 20 cm above the cot + a single 50 mg/kg oral dose of clofibrate <u>Phototherapy group</u> 4 special blue lamps (Phillips) 20 cm above the cot
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Outcomes	Duration of phototherapy Adverse effects
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Notes	Phototherapy stopped after bilirubin was below 14 mg/dL
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Risk of bias

Bias	Authors' judgement	Support for judgement
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Fallah 2012 (Continued)

Random sequence generation (selection bias)	Low risk	"Simple randomisation was by a computer generated random number list"
Allocation concealment (selection bias)	Low risk	List was prepared by "an investigator with no clinical involvement in the trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Patients and physicians allocated to the intervention group were aware of the allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Outcome assessors and data analysts were kept blinded to the allocation"

Ghotbi 2009

Methods	Design: CCT Blinding: not reported Randomisation: alternation Follow-up: not reported <u>Inclusion criteria</u> Healthy breastfed babies GA: 38 to 41 weeks Birthweight 2500 to 4000 g TSB 14 to 19.9 mg/dL <u>Exclusion criteria</u> Dehydration Infection ABO or Rh incompatibility G6PD deficiency Conjugated bilirubin above 2 mg/dL or exceeding 15% of TSB Congenital anomalies
Participants	<u>Phototherapy plus clofibrate group</u> Gender: 26 male, 19 female Mean age at baseline: 120 ± 36 hours Mean bilirubin at baseline: 18.4 ± 1.4 mg/dL Mean GA at birth: not reported Mean birthweight: 3190 ± 268 g <u>Phototherapy group</u> Gender: 24 male, 21 female Mean age at baseline: 134 ± 50 hours Mean bilirubin at baseline: 18.4 ± 1.8 mg/dL Mean GA at birth: not reported Mean birthweight: 3151 ± 289 g

Ghotbi 2009 (Continued)

Interventions	<p><u>Phototherapy plus clofibrate group</u></p> <p>4 special white 420 to 480 nm lamps being used less than 240 hours and adjusted to about 30 cm above neonate +</p> <p>single dose of 100 mg/kg clofibrate</p> <p><u>Phototherapy group</u></p> <p>4 special white 420 to 480 nm lamps being used less than 240 hours and adjusted to about 30 cm above neonate</p>
Outcomes	TSB and indirect bilirubin were measured every 12 hours to the end of phototherapy
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Habibi 2012

Methods	<p>Design: RCT</p> <p>Blinding: not reported</p> <p>Randomisation: random numbers table</p> <p>Follow-up: not stated</p> <p><u>Inclusion criteria</u></p> <p>Term neonate (GA 38 to 41 weeks)</p> <p>Weight: 2500 to 4000 g</p> <p>Age: 2 to 7 days</p> <p>Serum total bilirubin level: 17 to 26 mg/dL with priority of unconjugated bilirubin</p> <p>Level of direct bilirubin: less than 2 mg/dL or less than 15% of TSB</p> <p>Exclusive breastfeeding</p> <p><u>Exclusion criteria</u></p> <p>Premature neonates</p> <p>Sepsis</p> <p>Meningitis</p> <p>Congenital anomalies</p>
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Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia (Review)

Habibi 2012 (Continued)

	Dehydration Haemolytic diseases Conjugated hyperbilirubinaemia
Participants	<u>Phototherapy plus clofibrate group</u> Gender: 15 male, 11 female Mean age at baseline: 3.3 ± 1.1 days Mean bilirubin at baseline: 20.78 ± 2.38 mg/dL Mean GA at birth: not reported Mean Birthweight: 3057 ± 301 g <u>Phototherapy group</u> Gender: 15 male, 11 female Mean age at baseline: 3.19 ± 0.98 days Mean bilirubin at baseline: 20.52 ± 2.44 mg/dL Mean GA at birth: not reported Mean birthweight: 3105 ± 337 g
Interventions	<u>Phototherapy plus clofibrate group</u> 8 lamped set (Tusan model using 20-watt Phillips bulbs) and adjusted to 25 cm above the infant's cot + a single oral dose of clofibrate (100 mg/kg birthweight) <u>Phototherapy group</u> 8 lamped set (Tusan model using 20-watt Phillips bulbs) and adjusted to 25 cm above the infant's cot
Outcomes	Duration of phototherapy Bilirubin level Adverse effects
Notes	Phototherapy stopped once bilirubin level reached 14 mg/dL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Placing in case or control, groups was based on a random numbers table"
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Mohammadzadeh 2005

Methods	<p>Design: RCT Blinding: not reported Randomisation: random numbers table Follow-up: 2 days</p> <p><u>Inclusion criteria</u> Healthy, breast fed neonates</p> <p>Delivered between 38th and 41 weeks GA after an uncomplicated pregnancy</p> <p>TSB 17 and 29.9 mg/dL</p> <p><u>Exclusion criteria</u> Any congenital anomaly Haemolytic disease (Rh or ABO incompatibility and a positive Coombs' test) Infection (congenital or acquired) Dehydration G6PD deficiency Conjugated bilirubin > 2.0 mg/dL or exceeding 15% of TSB</p>
Participants	<p><u>Phototherapy plus clofibrate group</u></p> <p>Gender: 20 male, 10 female Mean age at baseline: 235 ± 99 hours Mean bilirubin at baseline: 22.35 ± 3.35 mg/dL Mean GA at birth: 38.7 ± 0.85 weeks Mean birthweight: 3257 ± 473.87 g</p> <p><u>Phototherapy group</u></p> <p>Gender: 14 male, 16 female Mean age at baseline: 197 ± 88 hours Mean bilirubin at baseline: 23.81 ± 3.38 mg/dL Mean GA at birth: 38.76 ± 0.89 weeks Mean birthweight: 3262 ± 496.02 g</p>
Interventions	<p><u>Phototherapy plus clofibrate group</u> 6 special white lamps and adjusted to 20 cm above the infant's cots. The lamps were changed regularly after 250 hours of usage plus</p> <p>a single oral dose of clofibrate (100 mg/kg birthweight)</p> <p><u>Phototherapy group</u> 6 special white lamps and adjusted to 20 cm above the infant's cots. The lamps were changed regularly after 250 hours of usage</p>
Outcomes	<p>Bilirubin levels Duration of phototherapy Number of exchange transfusions needed Adverse effects of clofibrate</p>
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a table of random numbers"

Mohammadzadeh 2005 (Continued)

Allocation concealment (selection bias)	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Mohammadzadeh 2009

Methods	Design: RCT Blinding: double-blind Randomisation: not reported Follow-up: 2 days <u>Inclusion criteria</u> Healthy, breastfed Birthweight: less than 2500 g <u>Exclusion criteria</u> Any congenital anomaly Haemolytic disease (Rh or ABO incompatibility and a positive Coombs' test) Infection (congenital or acquired) Dehydration G6PD deficiency History of phenobarbital intake either by mother or infant
Participants	<u>Phototherapy plus clofibrate group</u> Gender: 12 male, 18 female Mean age at baseline: 209 ± 138 hours Mean bilirubin at baseline: 22.7 ± 5.28 mg/dL Mean GA at birth: 31.46 ± 1.44 weeks Mean birthweight: 2186 ± 243.3 g <u>Phototherapy group</u> Gender: 20 male, 10 female Mean age at baseline: 230 ± 122 hours Mean bilirubin at baseline: 19.5 ± 4.7 mg/dL Mean GA at birth: 31.5 ± 1.6 weeks Mean birthweight: 2042 ± 386.5 g
Interventions	<u>Phototherapy plus clofibrate group</u> 4 special blue lamps (Philips Co., Germany) and adjusted to 25 cm above the infants' cots plus single-dose clofibrate 100 mg/kg via orogastric tube <u>Phototherapy group</u> 4 special blue lamps (Philips Co., Germany) and adjusted to 25 cm above the infants' cots plus

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Mohammadzadeh 2009 (Continued)

sterile water as clofibrate volume via orogastric tube

Outcomes	Bilirubin levels Duration of phototherapy Number of exchange transfusions needed Adverse effects of clofibrate Rebound jaundice
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	Low risk	"The clofibrate and placebo were coded, nor physician neither laboratories known about type of treatment and selection of case and control group was randomly"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The clofibrate and placebo were coded, nor physician neither laboratories known about type of treatment and selection of case and control group was randomly"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The clofibrate and placebo were coded, nor physician neither laboratories known about type of treatment and selection of case and control group was randomly"

Moslehi 2007

Methods	Design: RCT Blinding: not reported Randomisation: random numbers table Follow-up: 2 days <u>Inclusion criteria</u> Healthy, full term neonates (between 38th and 41st week of GA) Birthweight of 2500 to 3500 g Breastfed TSB: 17 to 24.9 mg/dL <u>Exclusion criteria</u> Presence of any congenital anomaly Haemolytic disease (Rh or ABO incompatibility and a positive Coombs' test) infection (congenital or acquired) Dehydration G6PD deficiency Conjugated bilirubin > 2.0 mg/dL
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Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia (Review)

Moslehi 2007 (Continued)

TSB > 25 mg/dL

Participants	<p><u>Phototherapy plus clofibrate group 1 (50 mg/kg)</u></p> <p>Gender: 14 male, 16 female Mean age at baseline: 124 ± 49 hours Mean bilirubin at baseline: 17.6 ± 1.5 mg/dL Mean GA at birth: 38.8 ± 1.9 weeks Mean birthweight: 2525 ± 628 g</p> <p><u>Phototherapy plus clofibrate group 2 (25 mg/kg)</u></p> <p>Gender: 17 male, 13 female Mean age at baseline: 126 ± 48 hours Mean bilirubin at baseline: 17.7 ± 1.3 mg/dL Mean GA at birth: 38.4 ± 1.5 weeks Mean birthweight: 2564 ± 428 g</p> <p><u>Phototherapy group</u></p> <p>Gender: 16 male, 14 female Mean age at baseline: 127 ± 45 hours Mean bilirubin at baseline: 17.6 ± 1.4 mg/dL Mean GA at birth: 39.3 ± 1.2 weeks Mean birthweight: 2539 ± 585 g</p>
Interventions	<p><u>Phototherapy plus clofibrate group 1</u></p> <p>6 special white lamps 20 cm above the infant's cot. The lamps were changed regularly after 250 hours of usage plus</p> <p>single oral dose of clofibrate (50 mg/kg) in a mixture of corn-oil 20 minutes before breastfeeding</p> <p><u>Phototherapy plus clofibrate group 2</u></p> <p>6 special white lamps 20 cm above the infant's cot. The lamps were changed regularly after 250 hours of usage plus</p> <p>single oral dose of clofibrate (25 mg/kg) in a mixture of corn-oil 20 minutes before breastfeeding</p> <p><u>Phototherapy group</u></p> <p>6 special white lamps 20 cm above the infant's cot. The lamps were changed regularly after 250 hours of usage</p>
Outcomes	<p>Bilirubin levels Duration of phototherapy Adverse effects of clofibrate</p>
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a table of random numbers."
Allocation concealment (selection bias)	High risk	Not reported

Moslehi 2007 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Sakha 2009

Methods	<p>Design: RCT Blinding: double-blind Randomisation: random-numbers table Follow-up: 1 week</p> <p><u>Inclusion criteria</u> Healthy late preterm newborns (GA 34 to 37 weeks) Non-haemolytic jaundice Did not need urgent exchange transfusion</p> <p><u>Exclusion criteria:</u> Major congenital anomalies Haemolytic disorders G6PD deficiency diagnosed by qualitative, visual, colorimetric test Sepsis Significant accompanying illness requiring NICU admission</p>
Participants	<p><u>Phototherapy plus clofibrate group</u></p> <p>Gender: 20 male, 10 female Mean age at baseline: 149 ± 63 hours Mean bilirubin at baseline: 20.05 ± 2.82 mg/dL Mean GA at birth: 35.04 ± 1.56 weeks Mean birthweight: not reported</p> <p><u>Phototherapy group</u></p> <p>Gender: 18 male, 12 female Mean age at baseline: 145 ± 75 hours Mean bilirubin at baseline: 19.72 ± 1.79 mg/dL Mean GA at birth: 35.16 ± 1.44 weeks Mean birthweight: not reported</p>
Interventions	<p><u>Phototherapy plus clofibrate group</u> 8 special blue fluorescent tubes labelled TL 52/20 w (Philips, Eindhoven, the Netherlands) adjusted at a 20-cm distance above the infant. Lamps of phototherapy units were changed regularly after 1500 hours of usage plus</p> <p>single dose of clofibrate 100 mg/kg was administered orally within 12 hours of admission</p> <p><u>Phototherapy group</u></p>

Sakha 2009 (Continued)

8 special blue fluorescent tubes labelled TL 52/20 w (Philips, Eindhoven, the Netherlands) adjusted at a 20-cm distance above the infant. Lamps of phototherapy units were changed regularly after 1500 hours of usage

Outcomes	Bilirubin levels Duration of phototherapy Adverse effects of clofibrate Rebound jaundice
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"By a random-number table sequence"
Allocation concealment (selection bias)	Low risk	"The allocation notes were kept in opaque sequentially numbered sealed envelopes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Based on the numerical order of sealed envelopes clofibrate or placebo was administered to patients by a nurse who was not involved in the care of the infant"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"By a physician who did not know the infant's group allocation. Duration of phototherapy was recorded by a nurse who was not involved in drug administration"

Sharafi 2010

Methods	Design: RCT Blinding: not reported Randomisation: not reported Follow-up: 2 days <u>Inclusion criteria:</u> Body weight: 2500 to 4000 g GA: 38 to 41 weeks Breastfed TSB: 14 to 20 mg/dL Postnatal age above 72 hours <u>Exclusion criteria:</u> ABO or Rh incompatibility G6PD deficiency Conjugated hyperbilirubinaemia Any concomitant disease
Participants	<u>Phototherapy plus clofibrate group</u> Gender: 12 males, 18 females Mean age at baseline: 163 ± 78 hours

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Sharafi 2010 (Continued)

Mean bilirubin at baseline: 17.24 ± 1.48 mg/dL
Mean GA at birth: not reported
Mean Birthweight: 3107 ± 394.89 g

Phototherapy group

Gender: 13 males, 17 females
Mean age at baseline: 158 ± 60 hours
Mean bilirubin at baseline: 17.42 ± 1.44 mg/dL
Mean GA at birth: not reported
Mean birthweight: 3150 ± 469.40 g

Interventions	<u>Phototherapy plus clofibrate group</u> 4 special blue tubes placed 40 cm above the infant as home phototherapy plus a single dose of 50 mg/kg clofibrate before starting phototherapy <u>Phototherapy group</u> 4 special blue tubes placed 40 cm above the infant as home phototherapy
Outcomes	Decrease in bilirubin Duration of phototherapy Adverse effects of clofibrate
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Zahedpasha 2007

Methods	Design: RCT Blinding: not reported Randomisation: not reported Follow-up: 1 week Inclusion criteria: Healthy, breast-fed
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Zahedpasha 2007 (Continued)

GA: 38 and 41 weeks
Uncomplicated pregnancy
TSB: 15 to 25 mg/dL
Body weight of ≥ 2500 g

Exclusion criteria:
Haemolytic disease
Rh or ABO incompatibility

Positive Coombs' test
G6PD deficiency
Conjugated bilirubin > 1.5 mg/dL or 15% of TSB
Dehydration
Infection (congenital or acquired)
History of phenobarbital intake either by mother or infant

Participants	<p><u>Phototherapy plus clofibrate group</u></p> <p>Gender: 14 male, 16 female Mean age at baseline: 136 ± 44 hours Mean bilirubin at baseline: 18.21 ± 1.85 mg/dL Mean GA at birth: not reported Mean birthweight: not reported</p> <p><u>Phototherapy group</u></p> <p>Gender: 14 male, 16 female Mean age at baseline: 153 ± 90 hours Mean bilirubin at baseline: 17.50 ± 2.34 mg/dL Mean GA at birth: not reported Mean birthweight: not reported</p>
Interventions	<p><u>Phototherapy plus clofibrate group</u></p> <p>4 special blue lamps (Philips Co., Germany) adjusted to 25 cm above the infant's cot plus single oral dose of clofibrate 100 mg/kg</p> <p><u>Phototherapy group</u></p> <p>4 special blue lamps (Philips Co., Germany) adjusted to 25 cm above the infant's cot</p> <p>The control group received distilled water in an equal amount and colour as placebo.</p>
Outcomes	<p>Decrease in bilirubin Duration of phototherapy Number of exchange transfusions needed Adverse effect</p>
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	High risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	All participants accounted for

Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia (Review)

Zahedpasha 2007 (Continued)

All outcomes

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Zahedpasha 2008

Methods	<p>Design: RCT Blinding: not reported Randomisation: not reported Follow-up: 7 days</p> <p><u>Inclusion criteria</u> G6PD-deficient jaundiced babies GA: 38 to 41 weeks</p> <p>Birthweight: ≥ 2500 g Born from an uncomplicated pregnancy TSB: ≥ 15 and < 20 mg/dL at > 48 hours after birth</p> <p><u>Exclusion criteria</u> Haemolytic disease (Rh or ABO incompatibility) Positive Coombs' test Conjugated bilirubin > 1.5 mg/dL or 15% of TSB Dehydration Infection (congenital or acquired)</p> <p>History of phenobarbital intake by mother or infant</p>
Participants	<p><u>Phototherapy plus clofibrate group</u></p> <p>Gender: not reported Mean age at baseline: 139 ± 61 hours Mean bilirubin at baseline: 18.40 ± 2.41 mg/dL Mean GA at birth: not reported Mean Birthweight: $3,195.2 \pm 403.7$ g</p> <p><u>Phototherapy group</u></p> <p>Gender: not reported Mean age at baseline: 105 ± 42 hours Mean bilirubin at baseline: 17.49 ± 1.03 mg/dL Mean GA at birth: not reported Mean birthweight: 3326.3 ± 553.6 g</p>
Interventions	<p><u>Phototherapy plus clofibrate group</u></p> <p>4 special blue lamps (made by Philips, Germany) adjusted to 25 cm above the infant cot plus a single oral dose of clofibrate (100 mg/kg)</p> <p><u>Phototherapy group</u></p> <p>4 special blue lamps (made by Philips, Germany) adjusted to 25 cm above the infant cot</p>

Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia (Review)

Zahedpasha 2008 (Continued)

Outcomes	Bilirubin levels Duration of phototherapy Number of exchange transfusions needed Adverse effects of clofibrate
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

CCT: clinical controlled trial; G6PD: glucose-6-phosphate dehydrogenase; GA: gestational age; NICU: neonatal intensive care unit; RCT: randomised controlled trial; TSB: total serum bilirubin.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bourget 1995	No placebo-control group
Flores 1996	Study examining the use of clofibrate to prevent hyperbilirubinaemia
Lindenbaum 1981	Study examining the use of clofibrate to prevent hyperbilirubinaemia
Lindenbaum 1985	Study examining the use of clofibrate to prevent hyperbilirubinaemia
Mohammadzadeh 2008	Study examining the use of clofibrate to prevent hyperbilirubinaemia
Morcos 2006	Case control study
Zahedpasha 2009	Study includes children with prolonged jaundice (Jaundice > 14 days of age) only

Characteristics of studies awaiting assessment [ordered by study ID]

Kumar 2017

Methods	This randomized controlled trial was done in the level III neonatal intensive care unit (NICU) of a tertiary care hospital. Ninety term neonates with unconjugated hyperbilirubinemia with serum bilirubin 15-25 mg/dl were randomized to either intervention group (single dose of clofibrate in a dose of 50 mg/kg prior to starting phototherapy) or standard care group (only phototherapy). Primary outcome was absolute fall in bilirubin by 48 h. Secondary outcomes were duration of phototherapy, absolute fall in bilirubin levels at 12, 24, 36, 48 h, need for exchange transfusion and incidence of side-effects.
Participants	
Interventions	
Outcomes	<p>After 48 h of intervention, significantly lower bilirubin levels were noted in the intervention group compared to standard care group with a mean difference of 7 mg/dl (95% CI 6.7 mg/dl to 7.2 mg/dl). Duration of</p> <p>phototherapy required was less in the intervention group compared to standard care group with mean difference of 23.82 h (95% CI 30.46 h to 17.18 h). Exchange transfusion was needed for 4 neonates in the standard care group and none in the intervention group. No side-effects were noted with clofibrate.</p>
Notes	

DATA AND ANALYSES

Comparison 1. Phototherapy + clofibrate 100 mg/kg versus phototherapy alone in preterm and term neonates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean total serum bilirubin (mg/dL) after 24 hours	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Preterm (< 37 weeks' GA)	2	128	Mean Difference (IV, Fixed, 95% CI)	0.55 [-0.48, 1.58]
1.2 Term (37 or more weeks' GA)	8	522	Mean Difference (IV, Fixed, 95% CI)	-2.14 [-2.53, -1.75]
2 Mean total serum bilirubin (mg/dL) after 48 hours	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Preterm (< 37 weeks' GA)	2	128	Mean Difference (IV, Fixed, 95% CI)	-1.37 [-2.19, -0.55]
2.2 Term (37 or more weeks' GA)	6	358	Mean Difference (IV, Fixed, 95% CI)	-1.82 [-2.25, -1.38]
3 Mean duration of phototherapy (hours)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Preterm (< 37 weeks' GA)	2	128	Mean Difference (IV, Fixed, 95% CI)	-23.82 [-30.46, -17.18]
3.2 Term (37 or more weeks' GA)	4	270	Mean Difference (IV, Fixed, 95% CI)	-25.40 [-28.94, -21.86]
4 Number of exchange transfusions needed	5	261	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.26]
5 Adverse effects of clofibrate	8	491	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Phototherapy + clofibrate 100 mg/kg versus phototherapy alone in preterm and term neonates, Outcome 1 Mean total serum bilirubin (mg/dL) after 24 hours.

Analysis 1.2. Comparison 1 Phototherapy + clofibrate 100 mg/kg versus phototherapy alone in preterm and term neonates, Outcome 2 Mean total serum bilirubin (mg/dL) after 48 hours.

Analysis 1.3. Comparison 1 Phototherapy + clofibrate 100 mg/kg versus phototherapy alone in preterm and term neonates, Outcome 3 Mean duration of phototherapy (hours).

Analysis 1.4. Comparison 1 Phototherapy + clofibrate 100 mg/kg versus phototherapy alone in preterm and term neonates, Outcome 4 Number of exchange transfusions needed.

Analysis 1.5. Comparison 1 Phototherapy + clofibrate 100 mg/kg versus phototherapy alone in preterm and term neonates, Outcome 5 Adverse effects of clofibrate.

Comparison 2. Phototherapy + clofibrate 50 mg/kg versus phototherapy alone in term neonates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean total serum bilirubin (mg/dL) after 24 hours	3	180	Mean Difference (IV, Fixed, 95% CI)	-3.54 [-3.96, -3.12]
2 Mean total serum bilirubin (mg/dL) after 48 hours	2	120	Mean Difference (IV, Fixed, 95% CI)	-3.41 [-3.91, -2.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Mean duration of phototherapy (hours)	2	120	Mean Difference (IV, Fixed, 95% CI)	-10.85 [-12.48, -9.23]
4 Number of exchange transfusion needed	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.87]
5 Adverse effects of clofibrate	3	180	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 99.95]

Analysis 2.1. Comparison 2 Phototherapy + clofibrate 50 mg/kg versus phototherapy alone in term neonates, Outcome 1 Mean total serum bilirubin (mg/dL) after 24 hours.

Analysis 2.2. Comparison 2 Phototherapy + clofibrate 50 mg/kg versus phototherapy alone in term neonates, Outcome 2 Mean total serum bilirubin (mg/dL) after 48 hours.

Analysis 2.3. Comparison 2 Phototherapy + clofibrate 50 mg/kg versus phototherapy alone in term neonates, Outcome 3 Mean duration of phototherapy (hours).

Analysis 2.4. Comparison 2 Phototherapy + clofibrate 50 mg/kg versus phototherapy alone in term neonates, Outcome 4 Number of exchange transfusion needed.

Analysis 2.5. Comparison 2 Phototherapy + clofibrate 50 mg/kg versus phototherapy alone in term neonates, Outcome 5 Adverse effects of clofibrate.

Comparison 3. Phototherapy + clofibrate 25 mg/kg versus phototherapy alone in term neonates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean total serum bilirubin (mg/dL) after 24 hours	1	60	Mean Difference (IV, Fixed, 95% CI)	-4.7 [-5.25, -4.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Mean duration of phototherapy (hours)	1	60	Mean Difference (IV, Fixed, 95% CI)	-11.10 [-12.73, -9.47]
3 Adverse effects of clofibrate	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Phototherapy + clofibrate 25 mg/kg versus phototherapy alone in term neonates, Outcome 1 Mean total serum bilirubin (mg/dL) after 24 hours.

Analysis 3.2. Comparison 3 Phototherapy + clofibrate 25 mg/kg versus phototherapy alone in term neonates, Outcome 2 Mean duration of phototherapy (hours).

Analysis 3.3. Comparison 3 Phototherapy + clofibrate 25 mg/kg versus phototherapy alone in term neonates, Outcome 3 Adverse effects of clofibrate.

APPENDICES

Appendix 1. Ovid MEDLINE(R) (1950 to February week 1 2010) search strategy

#	Searches	Results
1	randomised controlled trial.pt.	280513
2	controlled clinical trial.pt.	80002
3	DOUBLE BLIND METHOD/	103453
4	SINGLE BLIND METHOD/	13459
5	RANDOM ALLOCATION/	66578
6	RANDOMIZED CONTROLLED TRIALS/	64306
7	or/1-6	474442
8	((single or double or triple or treble) adj5 (blind\$ or mask\$)).tw,sh.	101460
9	clinical trial.pt.	452866
10	exp CLINICAL TRIAL/	591222
11	exp CLINICAL TRIALS AS TOPIC/	223082
12	(clinic\$ adj5 trial\$).tw,sh.	145934
13	PLACEBOS/	28300
14	placebo\$.tw,sh.	132216
15	random\$.tw,sh.	607002
16	or/8-15	1055967
17	or/7,16	1060637
18	META ANALYSIS/	23078
19	META ANALYSIS AS TOPIC/	9814
20	meta analysis.pt.	23078
21	(metaanaly\$ or meta-analy\$ or (meta adj analy\$)).tw,sh.	40640
22	(systematic\$ adj5 (review\$ or overview\$)).tw,sh.	23231
23	(methodologic\$ adj5 (review\$ or overview\$)).tw,sh.	2221
24	or/18-23	57629

(Continued)

25	review\$.pt.	1495163
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	36961
27	((hand or manual\$) adj2 search\$).tw.	3979
28	(electronic database\$ or bibliographic database\$ or computeri?ed database\$ or online database\$).tw,sh.	6466
29	(pooling or pooled or mantel haenszel).tw,sh.	32720
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1635
31	or/26-30	71991
32	and/25,31	32023
33	or/24,32	75297
34	letter.pt.	668939
35	case report.tw.	146613
36	comment.pt.	400828
37	editorial.pt.	249552
38	historical article.pt.	261273
39	or/34-38	1374875
40	17 not 39	1020563
41	33 not 39	71078
42	or/40-41	1057044
43	INFANT, PREMATURE/	33473
44	preterm\$.ti,ab.	31298
45	INFANT, NEWBORN/	426290
46	(newborn\$ or neonate\$).ti,ab.	141897
47	or/43-46	486369
48	HYPERBILIRUBINEMIA/	3433
49	HYPERBILIRUBINEMIA, NEONATAL/	255
50	hyperbilirubin?emia\$.ti.	2227
51	bilirubin?emia\$.ti.	147

(Continued)

52	((bilirubin\$ or hyperbilirubin\$) adj3 encephalopath\$.ti,ab.	313
53	exp JAUNDICE/	10036
54	jaundice\$.ti.	9666
55	KERNICTERUS/	917
56	kernicterus.ti,ab.	684
57	or/48-56	20622
58	CLOFIBRATE/	3592
59	clofibrate\$.ti,ab.	2821[r2]
60	or/58-59	4318
61	and/57,60	22
62	and/42,61	10

Appendix 2. The Cochrane Library (1st quarter 2010) search strategy

Clofibrat*
Atromid

Appendix 3. EMBASE (1980 to 2010 week 6) search strategy

#	Searches	Results
1	CLINICAL TRIALS/	577791
2	(clinic\$ adj5 trial\$).ti,ab,sh.	138910
3	SINGLE BLIND PROCEDURE/	9037
4	DOUBLE BLIND PROCEDURE/	76095
5	RANDOM ALLOCATION/	27508
6	CROSSOVER PROCEDURE/	22410
7	PLACEBO/	137708
8	placebo\$.ti,ab,sh.	190524
9	random\$.ti,ab,sh.	469120

(Continued)

10	RANDOMIZED CONTROLLED TRIALS/	181145
11	((single or double or triple or treble) adj (blind\$ or mask\$)).ti,ab,sh.	97844
12	randomi?ed control\$ trial\$.tw.	38829
13	or/1-12	943711
14	META ANALYSIS/	37104
15	((meta adj analy\$) or metaanalys\$ or meta-analy\$).ti,ab,sh.	49578
16	(systematic\$ adj5 (review\$ or overview\$)).ti,sh,ab.	33041
17	(methodologic\$ adj5 (review\$ or overview\$)).ti,ab,sh.	1866
18	or/14-17	70511
19	review.pt.	993257
20	(medline or medlars or embase).ab.	27767
21	(scisearch or science citation index).ab.	886
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.	11407
23	((hand or manual\$) adj2 search\$).tw.	3183
24	(electronic database\$ or bibliographic database\$ or computeri?ed database\$ or online database\$).tw.	5319
25	(pooling or pooled or mantel haenszel).tw.	27532
26	(peto or dersimonian or "der simonian" or fixed effect).tw.	1111
27	or/20-26	60512
28	and/19,27	22455
29	or/18,28	82263
30	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.	1845008
31	13 not 30	809185
32	29 not 31	38239
33	or/31-32	847424
34	PREMATURITY/	31811
35	preterm\$.ti,ab.	29096
36	NEWBORN/	186962

(Continued)

37	(newborn\$ or neonate\$).ti,ab.	103282
38	or/34-37	252955
39	HYPERBILIRUBINEMIA/	6367
40	NEWBORN JAUNDICE/	1918
41	hyperbilirubin?emi\$.ti.	1239
42	bilirubin?emi\$.ti.	18
43	(bilirubin\$ or hyperbilirubin\$).ti,ab.	19247
44	jaundice\$.ti.	3840
45	KERNICTERUS/	788
46	kernicterus.ti,ab.	439
47	or/39-46	26053
48	CLOFIBRATE/	5241
49	clofibrate\$.ti,ab.	2004
50	or/48-49	5545
51	and/47,50	81
52	and/33,51	19

Appendix 4. CINAHL Ebsco (14 May 14 2010) search strategy

#	Query	Limiters/Expanders	Last Run Via	Results
S23	S18 and S22	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	0
S22	S19 or S20 or S21	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	18
S21	TI (atromid*) or AB (atromid*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	0
S20	TI (clofibrate) or AB (clofibrate)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	14

(Continued)

S19	(MH "Clofibric Acid")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	4
S18	S5 and S17	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	548
S17	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	924
S16	(TI "kernicterus*")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	50
S15	MH KERNICTERUS	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	130
S14	(TI jaundice*)	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	358
S13	MH JAUNDICE	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	286
S12	(AB "hyperbilirubin*" N3 "encephalopath*")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	4
S11	(TI "hyperbilirubin*" N3 "encephalopath*")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	0
S10	(AB "bilirubin*" N3 "encephalopath*")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	30
S9	(TI "bilirubin*" N3 "encephalopath*")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	10
S8	(TI "bilirubinaemia" OR "bilirubinemia")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	7
S7	(TI "hyperbilirubinemia" or "hyperbilirubinaemia")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	225
S6	MH HYPER-BILIRUBINEMIA	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	269

(Continued)

S5	S1 or S2 or S3 or S4	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	52074
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	12020
S3	MH INFANT, NEW-BORN	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	45595
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6817
S1	MH INFANT, PRE-MATURE	Search modes - Find all my search terms	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	754

Appendix 5. Ovid MEDLINE(R) In-Process and other non-indexed citations (12 February 2010) search strategy

#	Searches	Results
1	(prematu\$ adj3 infant\$).ti,ab.	211
2	preterm\$.ti,ab.	863
3	(newborn\$ or neonate\$).ti,ab.	2464
4	or/1-3	3223
5	hyperbilirubin?emi\$.ti,ab.	96
6	bilirubin?emi\$.ti,ab.	2
7	bilirubin\$.ti,ab.	491
8	jaundice\$.ti,ab.	491
9	kernicterus.ti,ab.	8
10	or/5-9	957
11	and/4,10	85
12	clofibrate\$.ti,ab.	19
13	"atromid-s".ti,ab.	0

(Continued)

14

and/11-12

0

Appendix 6. Data extraction form

Study ID **Initials of person extracting data**

Type of report (e.g. peer reviewed journal article, full report, brief report, letter, unpublished data)

Language of report

Full citation

Design of study (e.g. controlled trial, cross-over trial)

Site of intervention (e.g. single site, multiple sites, country)

Setting of intervention (e.g. urban, rural, mixed)

Ethics committee approval

Age of participants (e.g. mean, SD, range)

Sex of participants

Ethnicity and other demographics of participants

Baseline characteristics

Mean GA:

Mean BW:

Mean TSB:

Inclusion criteria

(Continued)

Exclusion criteria

Description of intervention(s) (including control condition, placebo, treatment as usual etc.)

Duration of intervention(s)

Total number of participants randomised

Unit of allocation

Power calculation or sample size estimate

Prospectively stated outcome(s)

WHAT'S NEW

Date	Event	Description
10 January 2019	Review declared as stable	Clofibrate has been withdrawn from the market in some countries and is no longer in use in adults (the primary indication) because of safety concerns. As such, we will no longer be updating this review.

HISTORY

Protocol first published: Issue 3, 2011

Review first published: Issue 12, 2012

Date	Event	Description
25 October 2018	Amended	Units for serum bilirubin levels in "Data and analyses" corrected (should be mg/dL and NOT micromol/L as originally labelled).

CONTRIBUTIONS OF AUTHORS

HM: planned the review; selected studies, extracted data, entered data and analysed results.

MG: planned the review; selected studies, extracted data, entered data and analysed results.

RL: carried out searches.

JR: advised and commented on protocol and review and wrote the implications for practice and research.

DM: advised and commented on protocol and review and wrote the implications for practice and research.

DECLARATIONS OF INTEREST

MG: none known.

HM and RL: were members of NCC-WCH technical team responsible for NICE Neonatal Jaundice guideline.

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External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of participants:

In the protocol we stated "We will include neonates with prolonged hyperbilirubinaemia (greater than 14 days of age for term neonates and greater than 21 days of age for preterm neonates)".

We changed this in the full review and excluded one study that examined clofibrate plus phototherapy for prolonged jaundice.

NOTES

Clofibrate has been withdrawn from the market in some countries and is no longer in use in adults (the primary indication) because of safety concerns ([Oliver 1984](#)). As such, we will no longer be updating this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Clofibrate [*therapeutic use]; Combined Modality Therapy [methods]; Hyperbilirubinemia, Neonatal [*therapy]; Phototherapy [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn