NHS England

Evidence review: Zinc salts for Wilson disease

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First published: December 2018

Updated: Not applicable

Prepared by: The NICE Medicines and Technologies Programme on behalf of NHS England Specialised Commissioning

The content of this evidence review was up-to-date in September 2017. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Key points

Wilson disease is a rare inherited genetic disorder that occurs in about 1 in 30,000 people. In people with the disease, biliary excretion of copper is impaired leading to accumulation of copper in the liver, which causes toxicity. Eventually, copper is released into the bloodstream and deposited in extrahepatic tissues causing dysfunction of other organs including the central nervous system, eyes and kidneys. Wilson disease is fatal without treatment.

Zinc acetate dihydrate (Wilzin) is licensed for treating people with Wilson disease. The marketing authorisation was granted by the European Medicines Agency (EMA) in 2004. Other zinc salts have also been used to treat people with Wilson disease but are not licensed in the UK for this condition.

The evidence review includes 2 systematic reviews and 6 observational studies that assessed zinc for first-line treatment of symptoms of Wilson disease (alone or in combination with a chelating agent [penicillamine or trientine]), or for maintenance treatment of Wilson disease (following treatment with a chelating agent).

The evidence review concludes that there is a lack of high-quality evidence to estimate the relative treatment effects of the available treatments for Wilson disease.

The best available evidence suggests penicillamine or **zinc salt monotherapy** is effective for treating most people with **symptoms of Wilson disease**. There appears to be little difference between the treatments, although penicillamine might be preferable to zinc for people with predominantly hepatic symptoms and, because it works faster, for those who are acutely ill.

From the available evidence, a **combination of a chelating agent (penicillamine or trientine) plus a zinc salt** appears to be effective for treating most people with **symptoms of Wilson disease**. However, analyses suggest that penicillamine, trientine or zinc taken alone are more effective than combination treatment, and more people taking combination treatment experience adverse effects. No firm conclusions can be drawn; however, the results of the studies suggest that combination treatment should be considered only after monotherapy has failed to manage symptoms, and people should be carefully monitored for adverse effects.

Studies also suggest that **zinc salts alone** are effective as **maintenance treatment** for Wilson disease in people who have previously taken zinc salts in combination with penicillamine or trientine.

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1. Introduction

Background and current guidance

Wilson disease is a rare inherited genetic disorder that occurs in about 1 in 30,000 people. In people with the disease, biliary excretion of copper is impaired leading to accumulation of copper in the liver, which causes toxicity. Eventually, copper is released into the bloodstream and deposited in extrahepatic tissues causing dysfunction of other organs including the central nervous system, eyes and kidneys. Wilson disease is fatal without treatment (Wilson disease, Oxford Textbook of Medicine).

Symptoms of Wilson disease are usually non-specific but the condition should be considered in adults and children with unexplained liver disease and neurological or psychiatric symptoms. Typical presentation is in the second and third decade of life, most commonly with liver disease (ranging from asymptomatic hepatomegaly to fulminant hepatic failure) or a neuropsychiatric disorder (dystonia, dysarthria, Parkinsonian tremor or psychiatric symptoms). Family screening is used to identify relatives of people with Wilson disease who have not yet developed symptoms (Wilson disease, Oxford Textbook of Medicine).

Chelating agents (such as penicillamine or trientine), which bind to copper in the body and are subsequently excreted, are usually recommended first-line for treating Wilson disease. There is most experience world-wide with penicillamine; however, some people cannot tolerate it due to adverse effects and it may initially worsen neurological symptoms. Zinc, which inhibits absorption of copper, may be taken alone or in combination with a chelating agent. Lifelong treatment is required for Wilson disease to avoid recurrence of symptoms and liver failure. Liver transplantation may be required for fulminant hepatic failure and decompensated liver disease that is unresponsive to medical therapy (Wilson disease, Oxford Textbook of Medicine).

The European Association for the Study of the Liver (EASL) guideline on managing Wilson disease advises that there is a lack of high-quality evidence to estimate the relative treatment effects of the available medicines. This evidence review considers the best available evidence for zinc (used alone or in combination with chelating agents) for:

- first-line treatment of people with symptomatic Wilson disease
- maintenance treatment of people whose symptoms have stabilised or improved with a chelating agent, and
- second-line treatment of people who cannot tolerate penicillamine.

Product overview

Mode of action

Zinc is believed to interfere with the uptake of copper from the gastrointestinal tract by inducing metallothionein, a protein in the body that chelates with metals. Metallothionein has greater affinity for copper than for zinc and preferentially binds copper, preventing its absorption. Because copper also enters the gastrointestinal tract from saliva and gastric secretions, zinc treatment can generate a negative balance for copper, and remove stored copper from the body (EASL guideline on managing Wilson disease).

Regulatory status

Zinc acetate dihydrate (Wilzin) is licensed for treating people with Wilson disease. The marketing authorisation was granted by the European Medicines Agency (EMA) in 2004.

Although the license does not preclude its use, the summary of product characteristics (SPC) states that zinc acetate dihydrate alone is not recommended for the initial treatment of people with symptoms of Wilson disease because of its slow onset of action. People with symptoms should initially be treated with a chelating agent (penicillamine or trientine), alone or in combination with zinc acetate dihydrate. When copper levels are below toxic thresholds and the person is clinically stable, maintenance treatment with zinc acetate dihydrate alone can be considered. Zinc may also be used alone in people who are presymptomatic.

When switching from a chelating agent to zinc acetate dihydrate for maintenance therapy, the chelating agent should be taken along with the zinc for 2 to 3 weeks because this is the time it takes for zinc to block copper absorption completely. The 2 treatments should be administered at least 1 hour apart.

Other zinc salts, such as zinc sulfate and zinc gluconate, have also been used to treat people with Wilson disease. However, apart from zinc acetate dihydrate, no licensed zinc salts are available in the UK for this condition. In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the person and whether use of these zinc salts is appropriate outside their authorised indications. Supporting information and advice is also available from the GMC.

Dosing information

According to the SPC for Wilzin, the usual dosage of elemental zinc for adults is 50 mg (corresponding to 167.84 mg of zinc acetate dihydrate) 3 times daily, with a maximum dosage of 50 mg 5 times daily. Each dose must be taken on an empty stomach, at least 1 hour before or 2–3 hours after meals.

Lower dosages are recommended for children and pregnant women. The dosage should be adjusted in response to therapeutic monitoring, including plasma free copper and urinary excretion of copper.

Cost

Wilzin costs £132.00 for 250 x 25mg capsules and £242.00 for 250 x 50 mg capsules, excluding VAT (MIMS, June 2017).

2. Summary of results

A systematic review (1 randomised trial and 12 observational studies) and 1 observational study found penicillamine and zinc salts (zinc acetate or zinc sulfate) are effective **first-line monotherapy** for most people with **hepatic or neurological symptoms of Wilson disease** (74% of people with hepatic symptoms improved or became asymptomatic with penicillamine compared with 56% with zinc, and 81% of people with neurological symptoms improved or became asymptomatic with penicillamine compared with 90% with zinc). There

appears to be little difference between the treatments, although penicillamine might be preferable to zinc for people with predominantly hepatic symptoms. The systematic review found that early neurological deterioration was more common with penicillamine than with zinc salts. Adverse effects, including serious adverse effects that caused people to stop treatment, were also seen more often with penicillamine compared with zinc salts. However, the number of people taking zinc salts to treat symptoms was small, different disease presentations (hepatic or neurological) were not equally represented, and the studies have many other limitations. No studies comparing trientine and zinc salts alone for initial treatment of symptomatic Wilson disease met the inclusion criteria for this evidence review.

A systematic review (17 studies; design of individual studies not reported) and 1 additional observational study found that **first-line combination treatment with chelating agents (penicillamine or trientine) plus zinc salts** (zinc acetate or zinc sulfate) was effective for 60% of people or treatment blocks (the duration of therapy until the medication was changed or until the end of follow-up) with **hepatic or neurological symptoms of Wilson disease**. Combination treatment appeared to be more effective for people with neurological symptoms compared with hepatic symptoms. However, when results from the systematic review were compared with results from studies of monotherapies for Wilson disease, analyses suggested that combination treatment is less effective than penicillamine, trientine or zinc taken alone, and more people taking combination treatment experience adverse effects. In addition, mortality and liver transplantation may be more common with combination treatment compared with monotherapy (12.7% overall versus 6.6%), particularly for penicillamine plus zinc sulfate (16.3%). The overall quality of the evidence is low and only 3 studies assessed trientine plus zinc salts.

Three observational studies found that clinical signs and symptoms remained stable when **zinc salts alone** (zinc acetate or zinc sulfate) were taken as **maintenance treatment for Wilson disease** in people who had previously taken zinc salts in combination with a chelating agent. Most people in the studies had taken penicillamine rather than trientine.

No studies that met the inclusion criteria specifically considered the use of zinc salts for treating people who were intolerant of penicillamine. Although some of the studies included in this evidence review may have included small numbers of **people who could not tolerate penicillamine**, this was not stated explicitly and results were not reported for this subgroup of people.

In the studies, zinc salts commonly caused **adverse effects**, but these were generally mild gastrointestinal adverse effects, which did not require discontinuation of treatment. One observational study suggested that adverse effects of zinc sulfate may be severe in children. The study authors noted that zinc acetate may be better tolerated than zinc sulfate.

According to the summary of product characteristics for zinc acetate dihydrate, which is licensed for treating Wilson disease in the UK, the most common undesirable effect is gastric irritation (in between 1 in 10 and 1 in 100 people). Elevations of serum alkaline phosphatase, amylase and lipase are also common. Sideroblastic anaemia and leukopenia occur uncommonly with zinc acetate dihydrate (in between 1 in 100 and 1 in 1000 people).

Most of the studies included in the systematic reviews and individual studies in this evidence review are low-quality retrospective non-comparative observational studies, which are

susceptible to bias, confounding and other methodological problems. Observational studies cannot prove that Wilson disease improved because of zinc salts or other treatments; they can only suggest that zinc salts were associated with an improvement in the condition.

3. Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was provided by NHS England's Policy Working Group for the topic (see the literature search terms section for more information). The research questions for this evidence review are:

1. Are zinc salts an effective, safe and cost-effective **initial sole treatment for symptomatic people** with Wilson disease in comparison with penicillamine or trientine?
2. Is treatment with **zinc salts in combination with penicillamine or trientine** clinically effective, safe and cost-effective in people with Wilson disease who are intolerant to penicillamine, or as **initial treatment for symptomatic people**?
3. What is the evidence base for using long-term zinc salt **maintenance therapy** in people whose condition has stabilised and improved following treatment with trientine?
4. Is treatment with zinc salts clinically effective, safe and cost-effective in people with Wilson disease who are **intolerant of penicillamine**?

The searches for evidence to support the use of zinc for Wilson disease were undertaken by the NICE Guidance Information Services' team. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The NICE evidence summary: process guide (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the grade of evidence section for more information).

4. Summary of included studies

The evidence review includes 2 systematic reviews and 6 observational studies. The first systematic review (Wiggelinkhuizen et al. 2009; 1 randomised trial and 12 observational studies) assessed zinc salts or chelating agents as **monotherapy** for **initial treatment** of Wilson disease. The second systematic review (Chen et al. 2015; 17 observational studies) assessed zinc salts and a chelating agent in **combination** for **initial treatment** of Wilson disease.

Three of the observational studies also considered **initial treatment** of people with symptoms of Wilson disease (Czlonkowska et al. 2014, Chang et al. 2013 and Wiernicka et

al. 2013). The other 3 assessed zinc salts taken alone as **maintenance treatment** for Wilson disease following treatment with a chelating agent (Brewer et al. 2001, Shimizu et al. 2010 and Sinha et al 2008).

A summary of the included studies is shown in table 1 (see the evidence summary tables for full details). No studies that met the inclusion criteria specifically considered the use of zinc salts for treating people who were intolerant of penicillamine.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Zinc versus chelating agents as monotherapy for initial treatment of Wilson disease			
Wiggelinkhuizen et al. (2009) Systematic review (1 randomised trial and 12 observational studies)	429 people (mean age about 14 years in the efficacy population, n=284) with various presentations[a] of Wilson disease	Aimed to compare the efficacy and safety of first-line monotherapy with penicillamine, trientine, tetrathiomolybdate and zinc salts	Proportion of people reported to be 'asymptomatic', 'improved', 'unchanged', 'deteriorated' or 'dead' after at least 3 months' follow-up (mean 64 months for penicillamine and 81 months for zinc salts)
Czlonkowska et al. (2014) Retrospective observational study in Poland	143 people (median age about 27 years) with symptomatic[b] Wilson disease	Compared first-line monotherapy with penicillamine and zinc sulfate	The likelihood of remaining on the first-line therapy at the end of follow-up (median 4 years)
Wiernicka et al. (2013) Retrospective observational study in Poland	53 children (mean age 10 years) with hepatic symptoms of Wilson disease	Investigated the adverse effects of zinc sulfate (usually first-line monotherapy, n=50)	Adverse effects (median follow-up 83.3 weeks)
Zinc in combination with chelating agents for initial treatment of Wilson disease			
Chen et al. (2015) Systematic review (17 studies; design of individual studies not reported)	1,056 people (mean age 17.6 years) with various presentations[a] of Wilson disease	Considered the efficacy and safety of first-line combination treatment with a chelating agent and zinc salt, and compared the results with those for monotherapies obtained from other clinical studies	Proportion of people who found treatment 'effective' or whose symptoms 'improved' or were 'stable' with treatment, compared with those who found treatment 'ineffective' or whose symptoms 'worsened' or were 'unchanged' (mean follow-up 10.6 years)
Chang et al. (2013) Retrospective observational study in China	65 people (mean age 9 years) with symptomatic[b] Wilson disease	Evaluated combination treatment with low-dose penicillamine and high-dose zinc sulfate	Overall outcome in terms of improvement, stability or worsening of signs and symptoms (median follow-up 7.3 years)
Zinc alone for maintenance treatment of Wilson disease			

Brewer et al. (2001) Retrospective observational study in the US	34 children and young people (mean age 12 years) with various presentations[a] of Wilson disease.	Discussed the efficacy and safety of zinc acetate in 17 people using it as maintenance therapy	Overall outcome in terms of improvement, stability or worsening of signs and symptoms (mean follow-up 3.6 years)
Shimizu et al. (2010) Prospective observational study in Japan	37 people (mean age 23 years) with Wilson disease that was-controlled or stable following treatment with chelating agents or zinc for more than 24 weeks	Assessed maintenance treatment with zinc acetate	Overall outcome in terms of improvement, stability or worsening of signs and symptoms after 48 weeks' treatment
Sinha et al (2008) Retrospective observational study in India	45 people (mean age about 13 years) with Wilson disease treated with penicillamine plus zinc sulfate (mean duration 107.4 months)	Studied the effect of stopping treatment with penicillamine therapy and maintaining zinc acetate	Overall outcome in terms of improvement, stability or worsening of signs and symptoms (mean follow-up 27.2 months)
[a] Presymptomatic, or with predominantly hepatic or neurological symptoms [b] Hepatic, neurological or mixed presentation			

Details of the excluded studies are listed in the section on evidence selection.

5. Results

An overview of the results for clinical effectiveness and safety and tolerability can be found in the evidence summary tables.

Clinical effectiveness

Zinc salts taken alone as initial treatment for people with symptoms of Wilson disease

The systematic review by Wiggelinkhuizen et al. (2009) assessed subgroups of people according to their clinical presentation. It found that hepatic symptoms of Wilson disease resolved or improved in 73.7% (42/57) of people taking penicillamine alone over a mean of 64 months and 55.6% (5/9) of people taking zinc salts (zinc acetate or zinc sulfate) alone over a mean of 81 months. Neurological symptoms resolved or improved in 80.6% (58/72) of people taking penicillamine and in 90% (9/10) of people taking zinc salts. More people reported initial deterioration of neurological symptoms with penicillamine compared with zinc salts (5.7% [6/107] versus 0.8% [1/127] respectively). No statistical analyses of pooled results were reported because the studies included in the systematic review were heterogeneous.

No studies of trientine or tetrathiomolybdate therapy were included in the systematic review because no relatively large studies considering the efficacy of initial monotherapy with these agents were found.

After a median 4 years' follow-up, the retrospective observational study by Czlonkowska et al. (2014) generally found no statistically significant differences between penicillamine alone and zinc sulfate alone in the likelihood of remaining on first-line therapy or in overall therapeutic success in subgroups of people with neurological or hepatic symptoms of Wilson disease. There was also no statistically significant difference between the treatments in initial deterioration of neurological symptoms in the neurological subgroup. Nobody in the hepatic subgroup experienced initial deterioration of neurological symptoms.

The retrospective observational study Wiernicka et al. (2013) did not consider the efficacy of zinc salts.

Neither of the studies identified for this evidence review compared zinc and trientine monotherapies for the initial treatment of Wilson disease.

Zinc salts in combination with penicillamine or trientine as initial treatment for people with symptoms of Wilson disease

The systematic review by Chen et al. (2015) assessed the effectiveness of combination treatments over a mean follow-up of 10.6 years and compared this with the effectiveness of monotherapies obtained from analyses from other studies in Wilson disease. Most of the studies included in the systematic review assessed penicillamine plus zinc sulfate or another zinc salt; only 3/17 of the included studies assessed trientine plus a zinc salt. The systematic review did not compare combination treatment with penicillamine plus zinc with trientine plus zinc.

Chen et al. (2015) found that monotherapy with penicillamine (73.7% versus 60.4% respectively, p=0.005), trientine (82.6% versus 60.4% respectively, p<0.00001) or zinc salts (71.6% versus 60.4% respectively, p=0.03) was statistically significantly more effective than combination treatment with zinc and a chelating agent. Combination treatment was found to be more effective in people presenting with predominantly neurological symptoms compared with hepatic symptoms (78.6% compared with 47.1%, p=0.02).

In the retrospective observational study by Chang et al. (2013), over a median 7.3 years, 89.2% (58/65) of people taking low-dose penicillamine plus high-dose zinc sulfate improved or became stable. Four people needed a liver transplant. Nobody had significant neurological deterioration.

Zinc salts taken as maintenance therapy following treatment with a chelating agent

The retrospective observational study by Brewer et al. (2001) found that there was no deterioration in urine or plasma copper levels, or in speech, neurological or liver function during a mean 3.6 years' follow-up in 17 children primarily taking zinc acetate alone as maintenance therapy after a chelating agent. Statistically significant improvements in speech and neurological function scores were reported in the neurological subgroup, although these improvements were small and it is not known if they were clinically important. It is not known how many of the children previously took trientine compared with penicillamine.

In their prospective observational study, Shimizu et al. (2010) found that hepatic and neurological symptoms did not worsen in 37 people who took zinc acetate alone for 48 weeks after previously being stable on penicillamine or trientine (alone or in combination with other zinc salts), nor did any clinical signs or laboratory findings. Before being treated with zinc acetate, 9 people had hepatomegaly and this resolved in all of them at 16 weeks. Twelve people took trientine initially (alone or with zinc salts), but results for this subgroup are not reported separately.

When penicillamine was stopped in people taking combination treatment, the retrospective observational study by Sinha et al (2008) found that 97.7% (44/45) improved or remained stable with zinc sulfate alone. Only 1 person reported worsening (in dysarthria). Some statistically significant improvements in disability and impairment were reported with maintenance treatment, but the clinical significance of these is unclear. This study did not include anybody taking trientine plus zinc initially.

Zinc salts alone or in combination with chelating agents for people who are intolerant of penicillamine

No studies that met the inclusion criteria specifically considered the use of zinc salts for treating people who were intolerant of penicillamine. Although some of the studies included in this evidence review may have included small numbers of people who could not tolerate penicillamine, this was not stated explicitly and results were not reported for this subgroup of people.

Safety and tolerability

Zinc salts taken alone as initial treatment for people with symptoms of Wilson disease

The systematic review by Wiggelinkhuizen et al. (2009) found that adverse effects occurred in 24.4% (50/205) of people taking penicillamine and 12.5% (28/224) of people taking zinc salts (zinc acetate or zinc sulfate). Severe adverse effects requiring discontinuation of treatment occurred in 12.7% (26/205) of people taking penicillamine and 0.9% (2/224) of people taking zinc salts. No statistical analysis could be reported, and no studies were available comparing zinc with trientine or tetrathiomolybdate.

In the observational study by Czlonkowska et al. (2014), more people had adverse effects with penicillamine compared with zinc sulfate (15.3% [11/72] versus 2.6% [2/78], p=0.008). The difference was statistically significant.

Wiernicka et al. (2013) found that 39.6% (21/53) of children experienced adverse effects with zinc sulfate over a median 83.3 weeks. All symptoms were of gastrointestinal origin, including abdominal pain, nausea and vomiting. Gastroscopy was performed in 7 children (33.3%, 7/21) who experienced persistent and severe abdominal pain. They were found to have gastritis with ulcerations or erosion and 4 of the 7 children were switched to penicillamine because their symptoms were not relieved with proton pump inhibitors. Three children were switched to zinc acetate and their symptoms improved, including 2 who had previously been switched to penicillamine but had adverse effects with that treatment.

Zinc salts in combination with penicillamine or trientine as initial treatment for people with symptoms of Wilson disease

The systematic review by Chen et al. (2015) found an overall adverse effect rate of 35.8% with zinc plus a chelating agent. Inter-study analysis found more adverse effects with combination treatment compared with trientine alone (relative risk [RR] 1.67, 95% confidence interval [CI] 1.04 to 2.69) or zinc salts alone (RR 2.25, 95% CI 1.36 to 3.73), but not compared with penicillamine alone (RR 1.10, 95% CI 0.87 to 1.38). When the effectiveness of combination treatment was analysed according to clinical presentation, there was no statistically significant difference in adverse effects between the groups of people with hepatic and neurological presentations (41.7% versus 26.3% respectively, p=0.84), possibly due to the small sample size.

Pooled data suggest combination treatment had a higher mortality or transplant rate than monotherapy (p<0.001), but Chen et al. (2015) considered that this result may be subject to bias. A higher mortality or transplant rate was seen with penicillamine plus zinc sulfate compared with all other combinations (16.3% vs. 4.7%; RR 3.51, 95% CI 1.54 to 8.00), which was statistically significant.

In the observational study by Chang et al. (2013), penicillamine was discontinued due to adverse effects in 6/65 people taking penicillamine plus zinc. Abdominal discomfort initially occurred in 6/65 people taking high-dose zinc sulfate, but resolved after 1–2 months.

Zinc salts taken as maintenance therapy following treatment with a chelating agent

In the total population in the study by Brewer et al. (2001), 11.8% (4/34) of children had mild gastric irritation with zinc acetate, and it had a small but statistically significant adverse effect on the children's high-density lipoprotein/total cholesterol ratio.

Adverse effects were seen in 54.1% (20/37) of people taking zinc acetate in the study by Shimizu et al. (2010). However, they were mild and did not require discontinuation of treatment. The most frequent adverse effects were gastrointestinal symptoms (such as stomach discomfort, 16.2% [6/37]) and decreased blood iron levels (45.9% [17/37]).

No adverse effects were reported with zinc sulfate alone in the study by Sinha et al (2008).

Summary of product characteristics

According to the summary of product characteristics for zinc acetate dihydrate, which is licensed for treating Wilson disease in the UK, the most common undesirable effect is gastric irritation (in between 1 in 10 and 1 in 100 people). This is usually worst with the first morning dose and disappears after the first days of treatment. Delaying the first dose to mid-morning or taking the dose with a little protein (which interferes with absorption less than other food groups) usually relieves the symptoms. Elevations of serum alkaline phosphatase, amylase and lipase are also common, generally occurring after a few weeks of treatment, with levels usually returning to high-normal within the first 1–2 years of treatment. Sideroblastic anaemia and leukopenia occur uncommonly with zinc acetate dihydrate (in between 1 in 100 and 1 in 1000 people).

6. Discussion

Evidence strengths and limitations

It is difficult to undertake clinical trials in rare diseases because of the small number of eligible participants who are spread across a wide geographical area. This is especially true of heterogeneous diseases such as Wilson disease with a broad spectrum of subtypes (for example, different genetic mutations), clinical presentation (for example, hepatic, neurological, mixed or no symptoms), disease course and severity. The studies included in this evidence review are of low-quality and have many limitations that affect their application to clinical practice. More evidence from larger, longer-term, higher-quality trials may help to inform zinc's place in therapy. An overview of the quality assessment of each included study can be found in the grade of evidence tables.

The 2 systematic reviews mainly included uncontrolled observational studies, which have limitations inherent in their non-randomised design, especially around selection bias. The studies did not correct for possible confounders (including demographic factors, environmental factors, duration of disease, comorbidity, co-medication and dietary composition). Most included studies were descriptions of a single centre's experience with 1 particular medicine, which may emphasise the benefit of a specific therapy, with a high probability of observer bias. Also, because healthcare professionals might be more likely to use a tried and tested medicine in more seriously affected cases, zinc salts might be used less often in severely ill people, resulting in selection bias. In both systematic reviews, some subgroups analysed included only small numbers of people, particularly subgroups of people taking zinc, meaning these results may not be robust and comparisons may lack statistical power to detect differences in outcomes.

Wiggelinkhuizen et al. (2009) described their methods clearly and discussed the quality of the studies included in their systematic review, but Chen et al. (2015) did not. In Wiggelinkhuizen et al. (2009), heterogeneity between the included studies was considered likely to exist because of differences in the study populations, treatment pathways and outcome assessments and, although the results give some indication of the comparative efficacy and safety of treatment, statistical analysis of pooled results could not be performed. In the systematic review by Chen et al. (2015), it is unclear whether the study populations, treatment pathways and outcome assessments were similar between the studies, and no information on heterogeneity is reported; therefore, it is unclear whether the data was suitable to be pooled. The authors do, however, note that there may be bias in some of their interpretations of results due to the lack of substantial data and additional reports on combination treatments. They state that pooled data cannot be considered high-quality evidence for estimating the effectiveness and safety of combination treatments, and that their findings should be used to support treatment decisions only until more, and higher quality, evidence becomes available.

The 6 individual studies included in the evidence review were open-label, observational studies, 5 of which were retrospective and 1 was prospective. Retrospective studies lack prospectively defined systematic methods for data collection, treatment initiation, dosing and surveillance for adverse effects. As already noted, observational studies are susceptible to bias, confounding and other methodological problems. The only comparative study was a retrospective analysis, so no randomisation was used and allocation was not concealed; however, baseline characteristics appeared reasonably well-balanced across the treatments for each of the subgroups analysed. Treatment allocation and outcome assessment was not blinded in the studies. Most studies reflect the experience of single centres and some

include fewer than 50 people, which limits the available data. Less common adverse effects could have been missed and because these studies were observational, adverse effects may not have been recorded in detail in all cases.

Many of the studies included in the evidence review were undertaken in countries where populations, healthcare systems and treatment pathways differ from the UK (for example, Poland, the US, China, Japan and India) and they may not reflect UK practice. Nevertheless, all of the studies in the evidence review were considered to be direct studies focusing on people with the indication and characteristics of interest, and considering key efficacy and safety outcomes.

Treatment strategies for Wilson disease vary according to the presenting clinical features. Many of the analyses in the studies considered treatment outcomes according to clinical presentation; however, some analyses combined people with no symptoms, hepatic symptoms, neurological symptoms and both, and are, therefore, difficult to interpret and apply to clinical practice. The majority of patients in the UK are diagnosed and subsequently treated between childhood and middle age. Some of the studies in the evidence review include a broad age range, but others only included children and may not be applicable to people who present with symptoms later in adulthood.

Wilson disease is a lifelong condition but the studies included in this evidence review have generally been conducted over a relatively short period of time. A person's condition may take several years to deteriorate after stopping treatment (Scheinberg et al. 1987) and this should be taken into account when considering the results of studies of maintenance treatment following discontinuation of a chelating agent. In practice, clinical and biochemical markers are used to determine when a person's treatment may be changed to zinc maintenance therapy. Some of the studies included in this evidence review monitored biochemical parameters when treatment was changed to zinc maintenance therapy; however, the studies do not provide sufficient information on when or why treatment was switched in the participants to help determine the optimal clinical condition or biochemical levels at which a change from a chelating agent could be considered.

Other treatments

The EASL guideline on managing Wilson disease recommends that initial treatment for people with symptoms of Wilson disease should include a chelating agent (penicillamine or trientine). Zinc may have a role as a first-line therapy in people with neurological symptoms, and it is sometimes taken in combination with a chelating agent, or for maintenance treatment of Wilson disease, after a chelating agent. The guideline from the American Association for the Study of Liver Diseases makes similar treatment recommendations.

The EASL guideline recommends that the dose of elemental zinc is 150 mg/day in adults (and 75 mg/day in children who weigh less than 50 kg), administered in 3 divided doses, 30 minutes before meals (see the summary of product characteristics for more information for zinc acetate dihydrate). The guideline advises that the recommended maintenance dose of penicillamine for adults is usually 750–1500 mg/day in 2 or 3 divided doses (see the summary of product characteristics for more information on dosages licensed in the UK, for example, Distamine 250 mg, which differs slightly from the guidance) and typical dosages of trientine are 900–2700 mg/day in 2 or 3 divided doses, with 900–1500 mg/day used for

maintenance therapy. A trientine product is currently being evaluated for a license by the European Medicines Agency.

Costs of other treatments

The table shows the comparative costs of maintenance dosages for treating adults with Wilson disease for 28 days, using the dosage ranges in the EASL guideline on managing Wilson disease. The doses may differ from those licensed in the UK for some products. The costs are for the medicines only (excluding VAT) and do not include any local procurement discounts or any costs incurred, such as distribution costs.

Table 2 Costs of other treatment(s)/medicines name(s)

Treatment	Maintenance dosage[a]	Cost per unit	Cost of 28 days' treatment
Zinc acetate dihydrate	150 mg/day elemental zinc[b]	£242.00 for 250 x 50 mg capsules[c]	£81.31
Penicillamine	750–1500 mg/day	£88.77 for 56 x 250 mg tablets[d]	£133.15 to £266.31
Trientine dihydrochloride	900–1500 mg/day	£3,090.00 for 100 x 300 mg capsules[d]	£2,595.60 to £4,326.00

[a] Administered in divided doses
[b] Each capsule of Wilzin 50 mg contains 50 mg of elemental zinc corresponding to 167.84 mg of zinc acetate dihydrate
[c] Wilzin capsules: MIMS, July 2017.
[d] Drug tariff, July 2017

Current or estimated usage

The NHS prescription cost analysis for England 2016 reports that 637 community prescriptions for zinc acetate were dispensed in 2016, costing around £46,000 (net ingredient cost). For comparison, 11,294 community prescriptions for penicillamine were dispensed in 2016 costing about £1.2 million (net ingredient cost). Note that many of these prescriptions for penicillamine are likely to have been for treating people with rheumatoid arthritis or other immune disorders, rather than Wilson disease. Also, 369 community prescriptions for trientine dihydrochloride were dispensed in 2016, costing over £2 million (net ingredient cost). These data do not include hospital prescriptions.

7. Conclusion

Efficacy, safety, cost and patient factors should be taken into account when considering the likely place in therapy of zinc salts, as well as disease presentation in the individual, its nature and severity.

There is a lack of high-quality evidence to estimate the relative treatment effects of the available treatments for Wilson disease. The available evidence is of low quality and, although it may be used to guide practice, no firm conclusions can be drawn. Better quality large, prospective, multicentre, randomised controlled trials are needed, comparing treatments (particularly trientine, alone and in combination with zinc salts) for the initial

treatment, second-line and maintenance treatment of people with Wilson disease, and in people who cannot tolerate penicillamine.

The best available evidence suggests **penicillamine or zinc salt monotherapy** is effective for treating most people with **symptoms of Wilson disease**. There appears to be little difference between the treatments, although penicillamine might be preferable to zinc for people with predominantly hepatic symptoms and, because it works faster, for those who are acutely ill. Adverse effects and early neurological deterioration appear to be more common with penicillamine than with zinc salts. Therefore, zinc salts may be preferable for people who are less severely ill, when a fast onset of action is not required. None of the included studies compared trientine with zinc salts alone for treating people with symptomatic Wilson disease.

From the available evidence, **a chelating agent plus a zinc salt** appears to be effective for treating most people with **symptoms of Wilson disease**. However, analyses suggest that penicillamine, trientine or zinc taken alone are more effective than combination treatment, and more people taking combination treatment experience adverse effects. No firm conclusions can be drawn; however, the results of the studies suggest that combination treatment should be considered only after monotherapy has failed to manage symptoms, and people should be carefully monitored for adverse effects.

Studies also suggest that **zinc salts alone** are effective as **maintenance treatment for Wilson disease** in people who have previously taken zinc salts in combination with penicillamine or trientine.

No evidence was included looking specifically at **people who could not tolerate penicillamine**. More information on the best available evidence for trientine for treating Wilson disease is available in a separate evidence review.

Adverse effects of zinc salts are generally mild gastrointestinal adverse effects, which resolve as treatment continues. Adverse effects of zinc sulfate may sometimes be severe in children, who should be carefully monitored.

The studies included in the evidence review generally used zinc sulfate or zinc acetate. It is unclear whether 1 of these salts is more effective than the other. However, zinc acetate may be better tolerated than zinc sulfate. In the UK, zinc acetate dihydrate is the only zinc salt licensed for treatment of Wilson disease. Although the license does not preclude its use, the summary of product characteristics (SPC) states that it is not recommended for the initial treatment of people with symptoms of Wilson disease because of its slow onset of action.

The optimal dosage of zinc salts is also unclear from the studies, but the SPC for zinc acetate dihydrate lists dosages for the licensed indications. The dosage is generally adjusted according to therapeutic monitoring, including plasma free copper and urinary excretion of copper.

At about £80 per 28 days for maintenance treatment, the cost of zinc acetate is less than that of other treatments for Wilson disease. For comparison, the cost of penicillamine ranges from about £130 to £270 and the cost of trientine ranges from about £2,600 to

£4,300 per 28 days for maintenance treatment (excluding VAT, local procurement discounts and any costs incurred).

Zinc must be taken on an empty stomach, at least 1 hour before or 2–3 hours after meals. Penicillamine should also be taken on an empty stomach. Zinc is chelated by trientine and penicillamine and, therefore, cannot be taken at the same time of day. The restricted timing of multiple daily doses of treatments for Wilson disease mean it is unsurprising that compliance is reportedly poor (Ala et al. 2015).

8. Evidence summary table

Zinc versus chelating agents as monotherapy for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference 1: Wiggelinkhuizen et al. (2009)							
R1, systematic review including 1 prospective randomised trial and 12 observational studies (7 prospective non-comparative, 1 retrospective non-randomised comparative, and 4 retrospective non-comparative studies)	429 people newly diagnosed with Wilson disease Efficacy was evaluated in 199 people treated with penicillamine (mean age 14 years [range 1.5–52 years]) and 85 people (mean age 12.5 years [range 3–39 years]) treated with zinc salts Adverse effects were evaluated in 205 people taking penicillamine and 224 people taking zinc salts	Aimed to compare penicillamine, trientine, tetrathiomolybdate and zinc monotherapy for initial treatment of various clinical presentations (presymptomatic [n=136], or predominantly hepatic [n=66] or neurological [n=82] symptoms) of Wilson disease 7 studies assessed penicillamine only (usual dosage 1 g per day), 4 studies assessed zinc only (usual dosage 50–150 mg per day), and 2 studies assessed both of these Zinc salts used in the included studies were zinc acetate and zinc sulfate Mean follow-up was 64 months (range 3–228 months) for penicillamine and 81 months (range 3–323 months) for zinc salts	Primary Clinical effectiveness	Proportion of people reported to be 'asymptomatic', 'improved', 'unchanged', 'deteriorated' or 'dead' after at least 3 months' follow-up	Overall, treatment of hepatic symptoms was effective (asymptomatic or improved) in 73.7% (42/57) of people taking penicillamine and 55.6% (5/9) of people taking zinc salts Treatment of neurological symptoms was effective in 80.6% (58/72) of people taking penicillamine and 90% (9/10) people taking zinc salts No statistical analyses are reported	6/10 The research questions are stated but, as the study is based on observational studies it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any definitive conclusions. The methods are clearly described and the results are generalisable to the population considered in the evidence review	Direct study focusing on people with the indication and characteristics of interest
			Secondary Safety	Initial neurological deterioration	5.7% (6/107) of people reported neurological deterioration with penicillamine compared with 0.8% (1/127) of people taking zinc salts		
			Secondary Safety	Adverse effects	Adverse effects occurred in 24.4% (50/205) of people taking penicillamine and 12.5% (28/224) of people taking zinc salts		
			Secondary Safety	Severe adverse effects requiring treatment discontinuation	Severe adverse effects occurred in 12.7% (26/205) of people taking penicillamine and 0.9% (2/224) of people taking zinc salts		
Critical appraisal summary The systematic review addressed a clearly focused question and looked for published studies, excluding case reports and case series. It primarily included uncontrolled observational studies, but randomised controlled trials (RCTs) are often not feasible for rare diseases. All relevant studies appear to have been included, apart from studies not fully published or not in							

Zinc versus chelating agents as monotherapy for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
English, French or German. Key outcomes have been considered, and the results are applicable to the population being considered in this evidence review. The authors of the systematic review discussed the quality of the included studies, noting that most had an observational design with a profound risk of confounding. The included studies did not correct for possible confounders (including demographic factors, environmental factors, duration of disease, comorbidity, co-medication and dietary composition); therefore, most had a poor score for validity. Most included studies were descriptions of a single centre's experience with 1 particular medicine, which the authors of the systematic review noted is likely to emphasise the benefit of a specific therapy, with a high probability of observer bias. Also, because healthcare professionals might be more likely to use a tried and tested medicine in more seriously affected cases, zinc salts might be used less often in severely ill people, resulting in selection bias. Due to differences in the study populations, treatment pathways and outcome assessments, heterogeneity between the included studies was considered likely to exist. Although the results give some indication of the comparative efficacy and safety of treatment, statistical analysis of pooled results could not be performed because of heterogeneity between the studies. Zinc is recommended within its marketing authorisation for maintenance therapy for Wilson disease; therefore it has not usually been used as initial therapy, unlike penicillamine. The numbers of people taking zinc to treat symptoms is small. No studies of trientine or tetrathiomolybdate therapy were included because no relatively large studies considering the efficacy of initial monotherapy with these agents were found. The authors concluded that zinc therapy appears to be the best choice for presymptomatic people with Wilson disease because it is effective and has negligible adverse effects. Conversely, penicillamine might be better for acutely ill people with hepatic symptoms, because zinc might work too slowly for these people. In the low number of people with neurological symptoms treated with zinc, they concluded that zinc appears to be a better choice than penicillamine because severe side effects and initial deterioration were seen significantly less often with zinc salts compared with penicillamine. The authors stated that both trientine and tetrathiomolybdate have not been studied widely enough to make a proper judgement about the use of these agents in the initial treatment of Wilson disease.							
Study reference 2: Czlonkowska et al. (2014)							
P1, retrospective non-randomised comparative observational study	143 people newly diagnosed with symptomatic Wilson disease, 56 predominantly neurological symptoms (median age about 32 years [interquartile range 27–41 years]) and	Aimed to compare penicillamine (n=71) and zinc sulfate (n=72) as first-line monotherapy in people with newly diagnosed symptomatic Wilson disease in a single neurological centre in Poland The use of penicillamine was more common in the neurological subgroup (68.6% vs. 41.4% in	Primary Clinical effectiveness	Likelihood of remaining on the first-line therapy at the end of follow-up	There were no statistically significant differences between the treatments for the neurological or hepatic subgroups when standard analyses were undertaken. However, according to Kaplan–Meier analysis, the likelihood of remaining on first-line therapy was higher in people treated with zinc in the hepatic subgroup (p=0.028) Neurological subgroup: 20.0% (7/35) of people taking penicillamine changed therapy compared with 23.8% (5/21) of people taking	6/10 The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be	Direct study focusing on people with the indication and characteristics of interest

Zinc versus chelating agents as monotherapy for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
	87 predominantly hepatic symptoms (median age about 23 years [interquartile range19–32 years])	the hepatic subgroup, p=0.017) Baseline characteristics were generally similar between the treatments for the neurological and hepatic subgroups. Efficacy was analysed in the subgroups People taking penicillamine had more pronounced impairment of activities of daily living than those taking zinc sulfate. Median follow-up was 4 years (interquartile range 3–5 years)			zinc (p=0.748, not statistically significant) Hepatic subgroup: 30.6% (11/36) of people taking penicillamine changed therapy compared with 11.8% (6/51) of people taking zinc (p=0.054, not statistically significant)	considered hypothesis generating and cannot support any definitive conclusions. The methods are clearly described and the results are generalisable to the population considered in the evidence review	
			Primary Clinical effectiveness	Early neurological worsening within 180 days of the initiation of therapy Neurological worsening was assessed using the Unified Wilson Disease Rating Scale (UWDRS)	There was no statistically significant difference between the treatments in the neurological subgroup. 35.3% (12/34) of people taking penicillamine had early worsening compared with 19.0% (4/21) of people taking zinc sulfate (p=0.236) Nobody in the hepatic subgroup experienced early worsening		
			Secondary Clinical effectiveness	Overall therapeutic success at the end of follow-up (assessed using liver function tests and the UWDRS)	There were no statistically significant differences between the treatments Neurological subgroup: 82.8% (29/35) of people taking penicillamine were treated successfully compared with 71.4% (15/21) of people taking zinc sulfate (p=0.334) Hepatic subgroup: 94.4% (34/36) of people taking penicillamine were treated successfully compared with 94.1% (48/51) of people taking zinc sulfate (p=1.000)		

Zinc versus chelating agents as monotherapy for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
			Secondary Clinical effectiveness	Non-compliance (at least one 6-month period or at least two 3–6-month periods of not taking the medicine at all or diminishing the prescribed dose by more than half)	There was no significant difference between the treatments in non-compliance in the neurological subgroup (8.6% [3/35] of people taking penicillamine and 19.0% [4/21] of people taking zinc sulfate, p=0.406) In the hepatic subgroup, non-compliance was less common in people taking penicillamine (2.9% [1/35] compared with 19.6% [10/51] in the zinc sulfate group, p=0.024)		
			Secondary Safety	Death	In the neurological subgroup, 4 people (11.8%) taking penicillamine died, compared with 1 person (4.8%) taking zinc sulfate (p=0.639, not statistically significant) No people in the hepatic subgroup died		
			Secondary Safety	Drug-related adverse effects	Overall, statistically significantly more people had drug-related adverse effects with penicillamine compared with zinc sulfate (15.3% [11/72] versus 2.6% [2/78], p=0.008)		

Critical appraisal summary: This is an open-label, retrospective observational study and is, therefore, susceptible to bias, confounding and other methodological problems. Although it is a comparative study, it is a retrospective analysis so no randomisation was used and allocation was not concealed; however, baseline characteristics appeared reasonably well-balanced across the treatments for each of the subgroups analysed. Outcome assessment was not blinded. Dosages of the treatments were not reported.

The study reflects the experience of a single centre only. The authors note that this is a neurological centre and it is, therefore, possible that hepatic cases of Wilson disease are under-represented because severe cases are usually diagnosed and treated in a hepatology centre.

People taking penicillamine generally had more severe neurological symptoms or baseline hepatic dysfunction, despite the neurologists' reportedly discussing choice of treatment with the individual and not having a preference for this medicine. This may have been because people who believed more rapid treatment was required chose penicillamine, while people who were more concerned about adverse effects, chose zinc sulfate.

The study authors concluded that penicillamine and zinc sulfate are both effective for treating symptoms in people newly diagnosed with Wilson disease, and that neither medicine is clearly superior. They

Zinc versus chelating agents as monotherapy for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
concluded that zinc sulfate may be a reasonable alternative to penicillamine; however, better quality, large prospective multicentre studies are needed to confirm this.							
Study reference 3: Wiernicka et al. (2013)							
P1, retrospective non-comparative observational study	53 children with hepatic symptoms of Wilson disease (mean age at diagnosis 10 years [range 2.5–17 years]) treated with zinc sulfate	Investigated the adverse effects of zinc sulfate in children with Wilson disease in a single centre in Poland Zinc was used as monotherapy in 50 cases and in combination with penicillamine followed by zinc maintenance treatment in 3 cases The dosage of zinc depended upon the age of the child (45 mg once to 3 times daily) Median duration of treatment was 83.3 weeks (range 8–344 weeks)	Primary Safety	Adverse effects	39.6% (21/53) of children experienced adverse effects with zinc sulfate All symptoms were of gastrointestinal origin: abdominal pain, nausea or vomiting Gastroscopy was performed in 7 children (33.3%, 7/21) who experienced persistent and severe abdominal pain. Gastritis with ulcerations or erosion was evident in all cases 4 of the 7 children were switched to penicillamine because symptoms were not relieved with proton pump inhibitors 3 children were switched to zinc acetate and their symptoms improved. 2 of these had previously been switched to penicillamine but had adverse effects with that treatment	6/10 The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any definitive conclusions. The methods are described, and the results are generalisable to the population considered in the evidence review	Direct study focusing on people with the indication and characteristics of interest
Critical appraisal summary: This is a retrospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. The study reflects the experience of a single centre only. The study authors concluded that zinc sulfate appears to cause significant gastrointestinal adverse effects, and children being treated with this should be monitored closely.							

Zinc in combination with chelating agents for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference 4: Chen et al. (2015)							
R1, systematic review including 17 studies The designs of the 17 studies are not reported, but they appear to be observational studies	1,056 people with Wilson disease (mean age 17.6 years [range 6.0–38.5 years])	Aimed to verify whether combination treatments are effective and safe for people with different clinical presentations of Wilson disease (neurological 26.4%, hepatic 46.6%, mixed 17.6% and asymptomatic 9.3%) 11 studies assessed penicillamine plus zinc sulfate and 3 assessed penicillamine plus another zinc salt or an unknown zinc salt 3 studies assessed trientine plus zinc (1 each for zinc sulfate, zinc acetate, and another zinc salt or an unknown zinc salt) 1 study assessed an unknown chelator plus any zinc salt 1 study assessed 2 of these combinations The dosages of penicillamine varied and were often expressed as mg/kg, the dosage of trientine was usually 500–1000 mg daily, and the dosage of zinc salt was usually 50–100 mg daily (range 50–300 mg daily) Mean follow-up was 10.6 years	Primary Clinical effectiveness	Proportion of people who found treatment 'effective' or whose symptoms 'improved' or were 'stable' with treatment, compared with those who found treatment 'ineffective' or whose symptoms 'worsened' or were 'unchanged' (or synonyms of these terms) A comparative unit called a 'treatment block' was used. 1 treatment block is the duration of therapy until the medication was changed or until the end of follow-up	Of the 437 pooled treatment blocks, 264 responded positively to a combination treatment, an overall effectiveness rate of 60.4% (95% confidence interval [CI] 55.8% to 65.0%)	5/10 The research questions are stated but, as the study is based on observational studies it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any definitive conclusions. The methods are poorly described, but the results are generalisable to the population considered in the evidence review	Direct study focusing on people with the indication and characteristics of interest
			Secondary Clinical	Inter-study analysis of effectiveness with	Combination versus penicillamine alone: 60.4% versus 73.7% (relative risk [RR]		

Zinc in combination with chelating agents for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
		(range 1.0–25.0 years)	effectiveness	combination treatments compared with the 3 monotherapies	0.82, 95% CI 0.71 to 0.94; p=0.005) Combination versus trientine alone: 60.4% versus 82.6% (RR 0.73, 95% CI 0.65 to 0.82; p<0.00001) Combination versus zinc salts alone: 60.4% versus 71.6% (RR 0.84, 95% CI 0.72 to 0.98; p=0.03) (treatment blocks were used as events for comparison purposes, as for mortality and liver transplantation below)		
			Secondary Clinical effectiveness	Analysis of effectiveness with combination treatment according to clinical presentation	Hepatic versus neurological: 47.1% versus 78.6% of treatment blocks (RR 0.63, 95% CI 0.43 to 0.94; p=0.02)		
			Secondary Safety	Adverse effects	Of 271 treatment blocks, 97 resulted in adverse effects, an overall adverse effect rate of 35.8% (95% CI 30.1% to 41.5%) with combination treatment No statistically significant difference in adverse effect rate was found between hepatic and neurological presentations (41.7% versus 26.3%, p=0.84), possibly due to the small sample size Inter-study analysis found more adverse effects with combination treatment compared with trientine (RR 1.67, 95% CI		

Zinc in combination with chelating agents for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
					1.04 to 2.69) and compared with zinc salts (RR 2.25, 95% CI 1.36 to 3.73), but not compared with penicillamine (RR 1.10, 95% CI 0.87 to 1.38)		
			Secondary Safety	Mortality or liver transplantation combined	Of 2,239 people in 44 studies of monotherapy with the 4 most common treatments (penicillamine, trientine, zinc salts and combination treatment), 44 required liver transplants and 103 died, a mortality or transplant rate of 6.6% (95% CI 5.5% to 6.7%) Of 417 treatment blocks of combination treatment in this systematic review, 13 required liver transplants and 40 resulted in death, a mortality or transplant rate of 12.7% (95% CI 9.5% to 15.9%) Pooled data suggest combination treatment had a higher mortality or transplant rate than monotherapy ($p<0.001$), but this result may be subject to bias Mortality or transplant rates for hepatic and neurological presentations were difficult to determine due to insufficient data A higher mortality or transplant rate was seen with penicillamine plus zinc sulfate compared with all other combinations (16.3% vs. 4.7%; RR 3.51, 95% CI 1.54 to 8.00)		
Critical appraisal summary: The systematic review addressed a clearly focused question and looked for the right type of papers. It included prospective, retrospective, randomised and non-randomised controlled studies. However, the methods for the study are not clearly described. It appears that the majority of studies identified were observational studies (although this is not clearly reported). RCTs are							

Zinc in combination with chelating agents for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
often not feasible for rare diseases. Only the PubMed database was searched so it is unclear whether studies may have been missed. Published and English and Chinese-language studies were included. Key outcomes were considered, and the results are applicable to the population being considered in this evidence review. The authors of the systematic review state that the literature lacks rigorously designed studies and safety data on combination therapies using zinc salts and a chelating agent. Although they discuss the limitations of 3 commonly cited studies, the quality of the 17 included studies is not reported. Observational studies are subject to bias and confounding and the authors of the systematic review note that there may be bias in some of their interpretations of results due to the lack of substantial data and additional reports on combination treatments. It is unclear whether the study populations, treatment pathways and outcome assessments were similar between the studies, and no information on heterogeneity is reported; therefore, it is unclear whether the data was suitable to be pooled. The authors do, however, state that no firm recommendations can be drawn from the pooled data. They also note that Wilson disease is an intractable disease and individual people may have different responses to each of the most commonly used medications due to variance in disease genotypes and phenotypes. In summary, the systematic review found that, in people presenting with hepatic manifestations of Wilson disease, the effectiveness of combination treatment was only 47.1%, and 41.7% had adverse effects. Also, mortality and liver transplantation may be more common with combination treatment compared with monotherapy (12.7% overall versus 6.6%), particularly for penicillamine plus zinc sulfate (16.3%). Therefore, the authors conclude that the use of combination treatments involving zinc and a chelating agent should be carefully monitored with close clinical observations and frequent biochemical tests, especially for people with hepatic manifestations of Wilson disease. They stress that the pooled data cannot be considered high-quality evidence for estimating the effectiveness and safety of combination treatments, and that their findings should be used to support treatment decisions only until more and higher quality evidence becomes available.							
Study reference 5: Chang et al. (2013)							
P1, retrospective non-comparative observational study	65 people in China with symptomatic Wilson disease (mean age 9 years [range 5–13 years]; 44 hepatic, 6 neurological and 15 mixed presentation)	Evaluated long-term treatment with low-dose penicillamine (8–10 mg/kg daily) and high-dose zinc sulfate (100–300 mg daily depending on age) When clinical improvement occurred (mean duration 17.5 months), zinc sulfate was used alone Median follow-up was 7.3 years (range 0.5–18 years)	Primary/ secondary not specified Clinical effectiveness	Overall outcomes	89.2% (58/65) of people improved or became stable 4 people needed a liver transplant	6/10 The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and	Direct study focusing on people with the indication and characteristics of interest
			Primary/ secondary not specified Clinical	Liver function	Of people with hepatic symptoms, 78.2% (48/55) improved, 7.3% (4/55) were stable and 10.9% (6/55) worsened (2 because of poor compliance)		

Zinc in combination with chelating agents for initial treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
			effectiveness			cannot support any definitive conclusions. The methods are described and the results are generalisable to the population considered in the evidence review	
			Primary/ secondary not specified Clinical effectiveness	Neurological outcome	Improvement in neurological symptoms began a few months after initiation of therapy and was more evident in the first 2 years of treatment. Nobody had significant neurological deterioration. No quantitative data is reported		
			Primary/ secondary not specified Safety	Adverse effects	Penicillamine was discontinued due to adverse effects in 6 people No initial neurological deterioration was seen Initial abdominal discomfort occurred in 6 people taking zinc sulfate and resolved after 1–2 months		
Critical appraisal summary: This is a retrospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. The study reflects the experience of a single centre only. The study concludes that low-dose penicillamine and high-dose zinc sulfate is effective for initial treatment of people with Wilson disease, and appears to reduce adverse effects and neurological worsening with penicillamine.							

Zinc alone for maintenance treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**

Zinc alone for maintenance treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference 6: Brewer et al. (2001)							
P1, retrospective non-comparative observational study	34 children and young people (18 years or less, mean age at diagnosis 12 years [range 2.3–17.6 years]) with Wilson disease (17 presymptomatic, 10 neurological and 7 hepatic presentation) treated with zinc acetate	Reports the experience of a single US centre treating children and young people with Wilson disease with zinc acetate, and examines appropriate age-related dosages (from 25 mg twice daily to 50 mg 3 times daily) The 17 symptomatic children and young people were primarily treated with zinc as maintenance therapy during the study, following treatment with a chelating agent. The presymptomatic children are outside of the scope of the evidence review Mean number of years on zinc as a paediatric case 3.6 years (range 1.3–7.6 years)	Primary/ secondary not specified Clinical effectiveness	Overall outcomes	In the 17 symptomatic children primarily taking zinc acetate as maintenance therapy, there was no deterioration in urine or plasma copper levels, or in speech, neurological or liver function during follow-up Statistically significant improvements in speech and neurological function scores were reported in the neurological subgroup at year 1, although these improvements were small and it is not known if they were clinically important	6/10 The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any conclusions. The methods are described and the results are generalisable to the population considered in the evidence review	Direct study focusing on people with the indication and characteristics of interest
			Primary/ secondary not specified Safety	Adverse effects	In the total population, 11.8% (4/34) of children had mild gastric irritation Zinc acetate had a small but statistically significant adverse effect on the high-density lipoprotein/total cholesterol ratio		
Critical appraisal summary: This is a retrospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. The study reflects the experience with a small number of children only in a single centre. The study authors conclude that zinc acetate is effective and safe for the maintenance management of children and young people with Wilson disease, particularly those aged 10 years or more. More data is needed in very young children, and the adverse effects on lipid levels need to be studied further.							
Study reference 7: Shimizu et al. (2010)							

Zinc alone for maintenance treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
P1, prospective non-comparative observational study	37 people (mean age 23 years [range 4–51 years]) with Wilson disease (29 predominantly hepatic, 4 predominantly neurological and 4 mixed presentation) that was-controlled or stable following treatment with chelating agents (alone or with zinc salts) for more than 24 weeks 12/37 cases took trientine initially and 25/37 took penicillamine initially	Japanese study that assessed maintenance treatment with zinc acetate for 48 weeks The dosage of zinc acetate was age-dependent (ranging from 25 mg twice daily to 50 mg 3 times daily)	Primary/ secondary not specified Clinical effectiveness	Clinical course	9 people had hepatomegaly before being treated with zinc acetate, which resolved in all of them at 16 weeks Hepatic and neurological symptoms did not worsen in anybody, nor did any clinical signs or laboratory findings	6/10 The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any conclusions. The methods are described and the results are generalisable to the population considered in the evidence review	Direct study focusing on people with the indication and characteristics of interest
			Primary/ secondary not specified Safety	Adverse effects	Adverse effects were seen in 54.1% (20/37) of people, but were mild and did not require discontinuation of treatment The most frequent adverse effects were gastrointestinal symptoms (such as stomach discomfort, 16.2% [6/37]) and decreased blood iron levels (45.9% [17/37])		
Critical appraisal summary: This is a prospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. The study reflects the experience with a small number of Japanese people only. The study authors conclude that zinc acetate did not worsen any clinical signs or laboratory findings, and improved some symptoms of Wilson disease. Adverse effects were seen but were not severe. Therefore, the authors suggest that zinc acetate is an effective and safe agent for Japanese people with Wilson disease.							
Study reference 8: Sinha et al (2008)							

Zinc alone for maintenance treatment of Wilson disease							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
P1, retrospective non-comparative observational study	45 people (mean age at diagnosis 13 years [range 4–30 years]) with Wilson disease (40 hepatic and 5 neurological presentation) treated with penicillamine plus zinc sulfate (mean duration 107.4 months)	Studied the effect of stopping penicillamine in people with Wilson disease in India who were taking combination treatment 40 people had improved with combination treatment but 5 had not The dosage of zinc sulfate was high, ranging from 1,320–1,980 mg (300–450 mg elemental zinc) The mean duration of zinc sulfate maintenance therapy was 27.2 months (range 12–34 months)	Primary/ secondary not specified Clinical effectiveness	Overall outcomes	97.7% (44/45) of people improved or remained stable, and only 1 person reported worsening (in dysarthria) while taking zinc sulfate Statistically significant improvements in disability and impairment scores were reported with maintenance treatment with 2 different scales (both p=0.03). However, the clinical significance of these is unclear and no difference was seen with a third scale (p=0.4)	6/10 The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any conclusions. The methods are described and the results are generalisable to the population considered in the evidence review	Direct study focusing on people with the indication and characteristics of interest
			Primary/ secondary not specified Safety	Adverse effects	No adverse effects were reported with zinc sulfate alone		
Critical appraisal summary: This is a retrospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. The study reflects the experience of a single centre. The study authors conclude that withdrawal of penicillamine from combination treatment was effective, safe and economic for almost all cases, suggesting that zinc sulfate may be used as a preferred maintenance treatment for people with Wilson disease.							

9. Grade of evidence table

Zinc versus chelating agents as monotherapy for initial treatment of Wilson disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall therapeutic success	Wiggelinkhuizen et al. (2009)	6	Direct	B	This outcome describes the proportions of people whose Wilson disease was treated successfully. The systematic review of 13 studies by Wiggelinkhuizen et al. (2009) found that treatment of hepatic symptoms (symptoms affecting the liver) was effective in 73.7% of people taking penicillamine and 55.6% of people taking zinc salts. Treatment of neurological symptoms (symptoms affecting the nerves and nervous system) was effective in 80.6% of people taking penicillamine and 90% people taking zinc salts. All but 1 of the studies in the systematic review are low-quality observational studies in which participants were not randomised to treatments, which can lead to bias. The studies also did not correct for possible confounding factors that may have influenced the results (including demographic factors, environmental factors, duration of disease, comorbidity, co-medication and dietary composition). Due to differences in the study populations, treatment pathways and outcome assessments, the results of the studies could not be pooled. The number a people taking zinc to treat symptoms was small.
	Czlonkowska et al. (2014)	6	Direct		
Initial neurological deterioration	Wiggelinkhuizen et al. (2009)	6	Direct	B	Chelating agents, particularly penicillamine, can initially worsen neurological symptoms of Wilson disease. This outcome assesses this initial deterioration of symptoms affecting the nerves and nervous system. In the systematic review by Wiggelinkhuizen et al. (2009), 5.7% of people reported worsening of neurological symptoms with penicillamine compared with 0.8% of people taking zinc salts. All but 1 of the studies in the systematic review are low-quality observational studies in which participants were not randomised to treatments, which leads to bias. The studies also did not correct for possible confounding factors that may have influenced the results (including demographic factors, environmental factors, duration of disease, comorbidity, co-medication and dietary composition). Due to differences in the study populations, treatment pathways and outcome assessments, the results of the studies could not be pooled. The number a people taking zinc to treat symptoms was small.
	Czlonkowska et al. (2014)	6	Direct		
Likelihood of remaining on the first-line therapy at the end of follow-up	Czlonkowska et al. (2014)	6	Direct	C	This outcome considered how many people stayed on their first-line treatment and did not need to switch to another treatment because the first treatment did not work or caused side effects. Czlonkowska et al. (2014) found there were no statistically significant differences between penicillamine and zinc sulfate for subgroups of people with mainly neurological or hepatic symptoms when standard analyses were undertaken. However, according to another type of analysis, the likelihood of remaining on first-line therapy was

					higher in people treated with zinc in the group of people with hepatic symptoms (p=0.028). This study is an open-label, retrospective observational study and is, therefore, susceptible to bias, confounding and other methodological problems. Although it is a comparative study, it is a retrospective analysis so no randomisation was used and outcome assessment was not blinded.
Severe adverse effects requiring discontinuation of treatment	Wiggelinkhuizen et al. (2009)	6	Direct	C	This outcome considered how many people had to stop taking their treatment because of side effects. In the systematic review by Wiggelinkhuizen et al. (2009), severe side effects requiring treatment to be stopped occurred in 12.7% of people taking penicillamine and 0.9% of people taking zinc salts. All but 1 of the studies in the systematic review are low-quality observational studies in which participants were not randomised to treatments, which leads to bias. The studies also did not correct for possible confounding factors that may have influenced the results (including demographic factors, environmental factors, duration of disease, comorbidity, co-medication and dietary composition). Due to differences in the study populations, treatment pathways and outcome assessments, the results of the studies could not be pooled.
Adverse effects	Wiggelinkhuizen et al. (2009)	6	Direct	B	This outcome looked at how many people had side effects while they were taking treatment. In the systematic review by Wiggelinkhuizen et al. (2009), side effects occurred in 24.4% of people taking penicillamine and 12.5% of people taking zinc salts. All but 1 of the studies in the systematic review are low-quality observational studies in which participants were not randomised to treatments, which leads to bias. The studies also did not correct for possible confounding factors that may have influenced the results (including demographic factors, environmental factors, duration of disease, comorbidity, co-medication and dietary composition). Due to differences in the study populations, treatment pathways and outcome assessments, the results of the studies could not be pooled.
	Czlonkowska et al. (2014)	6	Direct		
	Wiernicka et al. (2013)	6	Direct		

Zinc in combination with chelating agents for initial treatment of Wilson disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**

Overall therapeutic success	Chen et al. (2015)	5	Direct	B	This outcome describes the proportions of people whose Wilson disease was treated successfully. The systematic review by Chen et al. (2015) found that, of the 437 pooled treatment blocks, 264 responded well to combination treatment with zinc and a chelating agent; an overall effectiveness rate of 60.4%. When compared with results from other studies looking at the efficacy of individual treatments for Wilson disease, combination treatment was found to be statistically significantly less effective than either penicillamine, trientine or zinc alone. Combination treatment was effective in only 47.1% of people with mainly hepatic symptoms, compared with 78.6% of people with mainly neurological symptoms. Most of the 17 studies in the systematic review appear to be observational studies, although this is not clearly stated, and details of the quality and limitations of the included studies are not provided. Observational studies are subject to bias and confounding and the authors of the systematic review note that there may be bias in some of their interpretations of results due to the lack of substantial data. It is unclear whether the study populations, treatment pathways and outcome assessments were similar between the studies, and no information on heterogeneity is reported; therefore, it is unclear whether the data was suitable to be pooled.
	Chang et al. (2013)	6	Direct		
Mortality or liver transplantation combined	Chen et al. (2015)	5	Direct	C	This outcome describes the proportions of people who died or whose disease progressed until they needed a liver transplant. The systematic review by Chen et al. (2015) found that, of 417 treatment blocks of combination treatment with zinc and a chelating agent, 13 required liver transplants and 40 resulted in death, a mortality or transplant rate of 12.7%. This compares with a mortality or transplant rate of 6.6% in studies of monotherapy with the 4 most common treatments, in which 44 out of 2,239 people required liver transplants and 103 died. A significantly higher mortality or transplant rate was seen with penicillamine plus zinc sulfate compared with all other groups (16.3% vs. 4.7%). Most of the 17 studies in the systematic review appear to be observational studies, although this is not clearly stated and details of the quality and limitations of the included studies are not provided. Observational studies are subject to bias and confounding and the authors of the systematic review note that there may be bias in some of their interpretations of results due to the lack of substantial data. It is unclear whether the study populations, treatment pathways and outcome assessments were similar between the studies, and no information on heterogeneity is reported; therefore, it is unclear whether the data was suitable to be pooled.
Adverse effects	Chen et al. (2015)	5	Direct	B	This outcome looks at how many people had side effects while they were taking treatment. The systematic review by Chen et al. (2015) found that, of 271 treatment blocks, 97 resulted in side effects with combination treatment with zinc and a chelating agent, an overall side effect rate of 35.8%. When the results were compared with those from studies of monotherapy for Wilson disease, side effects were statistically significantly more common with combination treatment than with trientine or zinc alone, but not penicillamine alone.

	Chang et al. (2013)	6	Direct		Most of the 17 studies in the systematic review appear to be observational studies, although this is not clearly stated and details of the quality and limitations of the included studies are not provided. Observational studies are subject to bias and confounding and the authors of the systematic review note that there may be bias in some of their interpretations of results due to the lack of substantial data. It is unclear whether the study populations, treatment pathways and outcome assessments were similar between the studies, and no information on heterogeneity is reported; therefore, it is unclear whether the data was suitable to be pooled.

Zinc alone for maintenance treatment of Wilson disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall therapeutic success	Brewer et al. (2001)	6	Direct	B	This outcome describes the proportions of people whose Wilson disease was treated successfully. In the prospective observational study by Shimizu et al. (2010), 9 people had hepatomegaly (an enlarged liver) before being treated with zinc acetate, which resolved in all of them at 16 weeks. Hepatic and neurological symptoms did not worsen in any of the 37 people in the study, nor did any clinical signs or laboratory findings. These 3 studies are non-comparative observational studies, which are susceptible to bias, confounding and other methodological problems. Only the study by Shimizu et al. (2010) was prospective; the others were retrospective. Outcome assessment was not blinded. The studies all reflect the experience of a small number of people only.
	Shimizu et al. (2010)	6	Direct		
	Sinha et al (2008)	6	Direct		
Adverse effects	Brewer et al. (2001)	6	Direct	B	This outcome looks at how many people had side effects while they were taking treatment. In Shimizu et al. (2010), side effects were seen in 54.1% of people taking zinc acetate, but were mild and did not require discontinuation of treatment. The most frequent side effects were gastrointestinal symptoms (such as stomach discomfort, 16.2%) and decreased blood iron levels (45.9%). These 3 studies are non-comparative observational studies, which are susceptible to bias, confounding and other methodological problems. Only the study by Shimizu et al. (2010) was prospective; the others were retrospective. Outcome assessment was not blinded. The studies all reflect the experience of a small number of people only.
	Shimizu et al. (2010)	6	Direct		
	Sinha et al (2008)	6	Direct		

10. Literature search terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	a) Patients with Wilson disease who are penicillamine intolerant after its use as first line treatment b) Patients with Wilson disease who have been on chelation therapy (trientine or penicillamine) for a period of time and have stabilized c) Patients presenting with symptomatic Wilson disease Subgroups where treatment may be applied differently d) Children within any of the above mentioned categories e) Pregnant women within any of the above categories
I – Intervention Which intervention, treatment or approach should be used?	a) Zinc salts used alone at different dosages b) Zinc salts in combination with penicillamine c) Zinc salts in combination with trientine
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	a) Reintroduction of penicillamine in selected patients in line with published experience/protocols. b) Trientine in patients intolerant to penicillamine c) Initial and/or long term penicillamine or trientine treatment Comparison will be based on clinical neurological or hepatic outcomes and analysis of copper balance/metabolism
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making: zinc salts as an alternative to trientine and penicillamine* Treatment failure as evidenced by clinical or biochemical deterioration, death, liver transplantation, or treatment withdrawal because of adverse effects of medication. *Important to decision-making:* Drug toxicity

	Copper deficiency Clinical and cost-effectiveness
Assumptions / limits applied to search	
Wilson disease is a rare disorder so it is important to consider all reports irrespective of study design, sample size, or date of publication (some papers are prior to 1990). We anticipate that there will be limited peer review articles in this field therefore other publications should be incorporated in the evidence review and listed by strength of evidence.	

11. Search strategy

Database: Medline
Platform: Ovid
Version: 1946 to May wk 4 2017
Search date: 01/06/2017
Number of results retrieved: A 106 B 275
Search strategy:
Database: Ovid MEDLINE(R) <1946 to May Week 4 2017>
Search Strategy:
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1 wilson* disease.tw. (4922)
2 ((kinnier-wilson* or kinnier wilson*) adj disease).tw. (1)
3 Hepatolenticular Degeneration/ (5451)
4 ((hepato-lenticular or hepatolenticular or lenticular) adj degenerat*).tw. (590)
5 ((hepato-neurologic* or hepatoneurologic*) adj degenerat*).tw. (0)
6 copper storage disease*.tw. (32)
7 or/1-6 (6580)
8 Zinc Acetate/ (229)
9 exp Zinc Compounds/ (10807)
10 (zinc or galzin or wilzin).tw. (84409)
11 or/8-10 (89586)
12 7 and 11 (499)
13 animals/ (6125262)
14 humans/ (16912119)
15 13 not 14 (4378365)
16 12 not 15 (461)
17 randomized controlled trial.pt. (464400)
18 randomized controlled trial/ (464400)
19 controlled clinical trial.pt. (94152)
20 random allocation/ (92938)
21 Placebos/ (35003)
22 clinical trial, phase ii/ or clinical trial, phase iii/ (43111)
23 meta-analysis.pt. (80909)
24 Network meta-analysis/ (92)
25 Meta-analysis as Topic/ (16081)
26 Review.pt. (2204556)
27 Review literature as Topic/ (6928)
28 (metaanaly* or metanaly* or (meta adj3 analy*)).tw. (94894)
29 (systematic* adj5 review*).tw. (89655)
30 or/17-29 (2926755)
31 16 and 30 (129)
32 limit 31 to english language (106)
33 16 not 31 (332)
34 limit 33 to english language (275)

Database: Medline in-process
Platform: Ovid
Version: May 31 2017
Search date: 01/06/2017
Number of results retrieved: A 14 B 14
Search strategy:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 31, 2017>
Search Strategy:

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1 wilson* disease.tw. (369)
2 ((kinnier-wilson* or kinnier wilson*) adj disease).tw. (0)
3 Hepatolenticular Degeneration/ (0)
4 ((hepato-lenticular or hepatolenticular or lenticular) adj degenerat*).tw. (18)
5 ((hepato-neurologic* or hepatoneurologic*) adj degenerat*).tw. (0)
6 copper storage disease*.tw. (2)
7 or/1-6 (377)
8 Zinc Acetate/ (0)
9 exp Zinc Compounds/ (0)
10 (zinc or galzin or wilzin).tw. (13407)
11 or/8-10 (13407)
12 7 and 11 (28)
13 limit 12 to english language (28)
14 (random* or placebo* or systematic* or meta*).tw. (396562)
15 13 and 14 (14)
16 13 not 15 (14)

Database: Medline epubs ahead of print
Platform: Ovid
Version: May 31 2017
Search date:01/06/2017
Number of results retrieved: A 4 B 3
Search strategy:
Database: Ovid MEDLINE(R) Epub Ahead of Print <May 31, 2017>
Search Strategy:

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1 wilson* disease.tw. (48)
2 ((kinnier-wilson* or kinnier wilson*) adj disease).tw. (0)
3 Hepatolenticular Degeneration/ (0)
4 ((hepato-lenticular or hepatolenticular or lenticular) adj degenerat*).tw. (1)
5 ((hepato-neurologic* or hepatoneurologic*) adj degenerat*).tw. (0)
6 copper storage disease*.tw. (0)
7 or/1-6 (49)
8 Zinc Acetate/ (0)
9 exp Zinc Compounds/ (0)
10 (zinc or galzin or wilzin).tw. (1611)
11 or/8-10 (1611)

12 7 and 11 (7)
13 limit 12 to english language (7)
14 (random* or placebo* or systematic* or meta*).tw. (68636)
15 13 and 14 (4)
16 13 not 15 (3)

Database: Embase
Platform: Ovid
Version: 1974 to 2017 Wk 22
Search date: 01/06/2017
Number of results retrieved: A 49 B 527
Search strategy:
Database: Embase <1974 to 2017 Week 22>
Search Strategy:
---
1 Wilson disease/ (9051)
2 wilson* disease.tw. (6887)
3 ((kinnier-wilson* or kinnier wilson*) adj disease).tw. (1)
4 ((hepato-lenticular or hepatolenticular or lenticular) adj degenerat*).tw. (518)
5 ((hepato-neurologic* or hepatoneurologic*) adj degenerat*).tw. (0)
6 copper storage disease*.tw. (35)
7 or/1-6 (9936)
8 zinc derivative/ (4505)
9 zinc acetate/ (1274)
10 (zinc or galzin or wilzin).tw. (113286)
11 or/8-10 (115994)
12 7 and 11 (949)
13 limit 12 to (conference abstract or conference paper or "conference review") (195)
14 12 not 13 (754)
15 limit 14 to english language (634)
16 Nonhuman/ (5127127)
17 Human/ (18262114)
18 16 not (16 and 17) (3957802)
19 15 not 18 (576)
20 randomized controlled trial/ (451092)
21 Randomization/ (73685)
22 Placebo/ (306295)
23 Crossover Procedure/ (51413)
24 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (1172608)
25 (random$ adj2 allocat$).tw. (33822)
26 placebo$.tw. (254703)
27 (crossover$ or (cross adj over$)).tw. (87955)
28 "Systematic Review"/ (138118)
29 Meta Analysis/ (126820)
30 (systematic* adj5 review*).tw. (138720)
31 (metaanaly* or metanaly* or (meta adj3 analy*)).tw. (146239)
32 or/20-31 (1832706)

33 19 and 32 (49)
34 19 not 32 (527)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – 6 of 12 June 2017
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 5 of 12 May 2017
HTA – 4 of 4 October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date:01/06/2017
Number of results retrieved: CDSR 0 ; DARE 1 ; CENTRAL 15 ; HTA 0 ; NHS EED.0
Search strategy:

Search Name:
Date Run: 01/06/17 09:00:31.987
Description:

ID SearchHits
#1 wilson* disease:ti,ab,kw (Word variations have been searched) 75
#2 (kinnier-wilson* or kinnier wilson*) near disease:ti,ab,kw (Word variations have been searched) 0
#3 MeSH descriptor: [Hepatolenticular Degeneration] this term only 23
#4 (hepato-lenticular or hepatolenticular or lenticular) near degenerat*:ti,ab,kw (Word variations have been searched) 27
#5 (hepato-neurologic* or hepatoneurologic*) near degenerat*:ti,ab,kw (Word variations have been searched) 0
#6 copper storage disease*:ti,ab,kw (Word variations have been searched) 4
#7 {or #1-#6} 86
#8 MeSH descriptor: [Zinc Acetate] this term only 22
#9 MeSH descriptor: [Zinc Compounds] explode all trees 433
#10 zinc or galzin or wilzin:ti,ab,kw (Word variations have been searched) 4137
#11 {or #8-#10} 4137
#12 #7 and #11 16

12. Evidence selection

The literature search identified 741 references (see search strategy for full details). These references were screened using their titles and abstracts, and the following were excluded: general reviews of Wilson disease; abstracts and conference reports; case studies; case series and other observational studies including fewer than 20 people taking zinc; studies not primarily considering the safety or efficacy of zinc; studies not considering outcomes of interest; studies describing the whole cohort, rather than relating outcomes to type of treatment; and studies included in 2 systematic reviews that were identified. Including the

systematic reviews, 15 references were obtained and assessed for relevance. Of these, 10 references (2 systematic reviews and 6 observational studies) are included in the evidence summary. The remaining 7 references were excluded and are listed in the following table.

Study reference	Reason for exclusion
Jablonska-Kaszewska I, Drobinska-Jurowiecka A, Dabrowska E et al. (2003) Results of treatment of Wilson's disease--own observations. Medical Science Monitor 9 Suppl 3: 9–14	Unable to source study
Kalita J, Kumar V, Chandra S et al. (2014) Worsening of Wilson disease following penicillamine therapy. European Neurology 71: 126–31	Little information on outcomes with zinc treatment
Litwin T, Dziezyc K, Karlinski M et al. (2015) Early neurological worsening in patients with Wilson's disease. Journal of the Neurological Sciences 355: 162–7	Further analysis of the study by Czlonkowska et al. 2014 offering little additional information
Pellecchia M T, Criscuolo C, Longo K et al. (2003) Clinical presentation and treatment of Wilson's disease: a single-centre experience. European Neurology 50: 48–52	Little information on outcomes with zinc treatment
Rodriguez B, Burguera J and Berenguer M (2012) Response to different therapeutic approaches in Wilson disease. A long-term follow up study. Annals of Hepatology 11: 907–14	Little information on outcomes with zinc treatment
Santiago R, Gottrand F, Debray D et al. (2015) Zinc therapy for Wilson disease in children in French pediatric centers. Journal of Pediatric Gastroenterology and Nutrition 61: 613–8	The majority of people were presymptomatic and no data was available on switching from trientine to zinc (switching from penicillamine to zinc in presymptomatic people is outside of the scope)
Svetel M, Pekmezovic T, Petrovic I et al. (2009) Long-term outcome in Serbian patients with Wilson disease. European Journal of Neurology 16: 852–7	Little information on outcomes with zinc treatment

13. References

Brewer GJ, Dick RD, Johnson VD et al. (2001) Treatment of Wilson's disease with zinc XVI: treatment during the pediatric years. Journal of Laboratory and Clinical Medicine 137: 191–8

Chang H, Xu A, Chen Z et al. (2013) Long-term effects of a combination of D-penicillamine and zinc salts in the treatment of Wilson's disease in children. Experimental & Therapeutic Medicine 5: 1129–32

Chen JC, Chuang CH, Wang JD et al. (2015) Combination therapy using chelating agent and zinc for Wilson's disease. Journal of Medical & Biological Engineering 35: 697–708

Czlonkowska A, Litwin T, Karlinski M et al. (2014) D-penicillamine versus zinc sulfate as first-line therapy for Wilson's disease. European Journal of Neurology 21: 599–606

Shimizu N, Fujiwara J, Ohnishi S et al. (2010) Effects of long-term zinc treatment in Japanese patients with Wilson disease: efficacy, stability, and copper metabolism. Translational Research: The Journal of Laboratory and Clinical Medicine 156: 350–7

Sinha S, and Taly AB (2008) Withdrawal of penicillamine from zinc sulphate-penicillamine maintenance therapy in Wilson's disease: promising, safe and cheap. Journal of the Neurological Sciences 264: 129–32

Wiernicka A, Janczyk W, Dadalski M et al. (2013) Gastrointestinal side effects in children with Wilson's disease treated with zinc sulphate. World Journal of Gastroenterology 19: 4356–62

Wiggelinkhuizen M, Tilanus ME, Bollen CW et al. (2009) Systematic review: clinical efficacy of chelator agents and zinc in the initial treatment of Wilson disease. Alimentary Pharmacology and Therapeutics 29: 947–58