

**NHS England**

**Evidence review: Trientine  
dihydrochloride for Wilson disease**



# NHS England

## Evidence review: Trientine dihydrochloride for Wilson disease

First published: December 2018

Updated: Not applicable

Prepared by: NICE on behalf of NHS England Specialised Commissioning

## Contents

|                                  |    |
|----------------------------------|----|
| 1. Introduction .....            | 4  |
| 2. Summary of results.....       | 5  |
| 3. Methodology.....              | 5  |
| 4. Results.....                  | 6  |
| 5. Discussion.....               | 7  |
| 6. Conclusion .....              | 11 |
| 7. Evidence Summary Tables.....  | 12 |
| 8. Grade of evidence tables..... | 20 |
| 9. Literature Search Terms ..... | 24 |
| 10. Search Strategy.....         | 25 |
| 11. Evidence selection.....      | 25 |
| 12. References.....              | 26 |

## 1. Introduction

Wilson disease is a rare inherited genetic disorder in which biliary excretion of copper is impaired. Copper accumulates in the liver and, subsequently, other organs including the central nervous system, eyes and kidneys. Children may be asymptomatic while copper accumulates. Symptoms of the disease are usually non-specific but it should be considered in people with unexplained liver disease and neurological or psychiatric symptoms. Wilson disease is fatal without treatment (Wilson disease, Oxford Textbook of Medicine).

The genetic defect, localized to arm 13q, has been shown to affect the copper-transporting adenosine triphosphatase (ATPase) gene (*ATP7B*) in the liver (Rodriguez-Castro et al 2015). Patients with Wilson disease more often initially present with hepatic manifestations when identified in the first decade of life as compared with more neuropsychiatric illness later, and the latter most commonly occurs during the third decade. The diagnosis is established by no individual test but requires the use of some combination of serum ceruloplasmin level, urinary copper excretion, presence of Kayser-Fleischer rings, and hepatic copper content when biopsy is required.

The natural history of Wilson disease may be considered in 4 stages, as follows:

- Stage I - The initial period of accumulation of copper within hepatic binding sites
- Stage II - The acute redistribution of copper within the liver and its release into the circulation
- Stage III - The chronic accumulation of copper in the brain and other extrahepatic tissue, with progressive and eventually fatal disease
- Stage IV - Restoration of copper balance by the use of long-term chelation therapy

There is a wide range in the age of onset including early-onset hepatic disease in a 3 year old child and late onset disease in two siblings in their 70s (Ala et al., 2007) with the mean age of onset of 15.9 years (Taly et al., 2007).

Worldwide, the incidence of Wilson disease is 10-30 million cases, and the heterozygote carrier rate is 1 case per 100 persons, with the genetic mutation frequency varying from 0.3-0.7%. In Japan, the rate is 1 case per 30,000 population, compared with 1 case per 100,000 population in Australia (Purchase 2013). The increased frequency in certain countries is due to high rates of consanguinity. The fulminant presentation of Wilson disease is more common in females than in males.

Chelating agents (such as penicillamine or trientine), which bond to copper in the body and are subsequently excreted, are recommended first line for treating Wilson disease. Zinc, which inhibits absorption of copper, may also be used. Lifelong treatment is required to avoid recurrence of symptoms and liver failure (Wilson disease, Oxford Textbook of Medicine).

Trientine dihydrochloride (also referred to as trientine hydrochloride or triethylenetetramine dihydrochloride) chelates with copper, forming a stable soluble

complex, which is excreted via the kidneys. Trientine dihydrochloride (manufactured by Univar) is licensed in the UK for treating Wilson disease in people who cannot tolerate penicillamine. First line use of trientine dihydrochloride is off-label.

Trientine dihydrochloride (manufactured by Univar) is available as 300 mg capsules. The adult dosage of trientine dihydrochloride is 1200–2400 mg (4–8 capsules) daily in 2 to 4 divided doses, preferably 30–60 minutes before meals.

The dosage in children is lower than for adults and depends on age and body weight. A typical dosage for initiating therapy is 600–1500 mg (2 to 5 capsules) daily, which should be adjusted according to clinical response

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 drugs. This evidence summary considers the best available evidence for trientine.

A phase 2 clinical trial is underway to evaluate the efficacy and safety of WTX01 administered for 24 weeks in newly diagnosed Wilson disease (WD) patients aged 18 and older with Nonceruloplasmin-bound copper (NCC) levels within or above the normal reference range at the time of enrollment (ClinicalTrials.gov Identifier: NCT02273596).

## 2. Summary of results

A retrospective observational study of 405 patients provides the best available evidence for using trientine dihydrochloride compared with penicillamine for Wilson disease. In the study, there were no statistically significant differences in the rates of hepatic and neurological improvement between trientine dihydrochloride and penicillamine. Hepatic signs and symptoms were reduced in about 90% of patients taking first line therapy and 70% of patients taking second line therapy with either drug. The proportion of patients experiencing improvement in neurological symptoms was lower (about 66% of patients taking first line therapy and 45% of patients taking second line therapy with either drug). More than a third of patients did not improve or became worse in both treatment groups.

Trientine was generally well tolerated. In the study, statistically significantly more patients discontinued treatment because of adverse events with penicillamine compared with trientine.

The other 6 studies included in the evidence review are smaller, including between 5 and 23 patients taking trientine. The evidence has significant limitations and better-quality studies are needed to compare the safety and efficacy of trientine, penicillamine and zinc for Wilson disease, and clarify their places in therapy.

## 3. Methodology

NICE Evidence summaries provide a summary of the published evidence for

selected medicines that are considered to be of significance to the NHS including new medicines, off-label use of licensed medicines and unlicensed medicines. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary and provide information for healthcare professionals to inform their decision making.

This evidence summary has been developed using the NICE's processes described in its integrated process statement for evidence summaries: new medicines. This statement sets out the process NICE uses to select topics for the evidence summaries, and explains how they are developed, quality assured and approved for publication.

This evidence summary considers the best available evidence for using trientine dihydrochloride for treating Wilson disease. It primarily looks at second line treatment of people who cannot tolerate penicillamine (the licensed indication), although studies of first line treatment are also included because of the limited amount and quality of evidence, and because trientine is sometimes used in this way (off-label).

In the searches undertaken for this evidence summary, studies of trientine for Wilson disease were included if they:

- were published between 1996 and July 2016 to capture studies that reflect current clinical practice
- were systematic reviews, randomised controlled trials (RCTs), prospective or retrospective cohort studies or case series
- considered people with Wilson disease taking any treatment (penicillamine, trientine or zinc) or trientine only, but not primarily other treatments
- included at least 5 people taking trientine (thereby excluding single case reports) primarily considered the efficacy or safety of individual treatments.

#### 4. Results

One systematic review was identified, which assessed the efficacy of chelating agents and zinc for treating Wilson disease (Wiggelinkhuizen et al. 2009). However, it found no studies on trientine that were suitable for inclusion.

Seven studies are included in this evidence review:

- 1 RCT comparing tetrathiomolybdate (an experimental chelating agent, which is not currently available) with trientine (Brewer et al. 2006)
- 2 prospective observational studies (Ala et al. 2015 and Askari et al. 2003)
- 4 retrospective observational studies (Arnon et al. 2007, Taylor et al. 2009, Walshe 2011 and Weiss et al. 2013).

## 5. Discussion

### **Clinical effectiveness**

The RCT investigating tetrathiomolybdate for neurological symptoms of Wilson disease provides limited evidence on the efficacy and safety of first line trientine plus zinc (Brewer et al. 2006). It found that 6/23 patients treated with trientine and zinc for 8 weeks (followed by zinc monotherapy) experienced worsening of their neurological symptoms (compared with 1/25 patients taking tetrathiomolybdate and zinc,  $p < 0.05$ ). No patients in either group reached the criteria for speech deterioration.

In their prospective observational study, Askari et al. (2003) found that 4 months' first line treatment with trientine plus zinc (followed by zinc monotherapy) improved liver function in 9 patients with Wilson disease and hepatic decompensation who were potential candidates for liver transplantation. After 6 months, all patients no longer met the criteria for liver transplantation. Ascites, fatigue, nausea and vomiting resolved with treatment.

Another prospective observational study investigated once-daily trientine in 8 patients with stable Wilson disease with liver involvement but mixed presentations (Ala et al. 2015). It found that, on changing from zinc ( $n=2$ ), conventionally dosed trientine ( $n=5$ ) or penicillamine ( $n=1$ ), physical examination remained unchanged and no new neurological signs were detected over 12 months.

The retrospective observational study by Weiss et al. (2013) provides the best available evidence for using trientine compared with penicillamine in patients with Wilson disease. It included 141 patients who took trientine monotherapy (36 first line and 105 second line) and outcomes in these patients were compared with outcomes in 326 patients who took penicillamine monotherapy (294 first line and 32 second line).

Weiss et al. (2013) found no statistically significant differences between trientine and penicillamine for treating hepatic signs and symptoms of Wilson disease when used first or second line. In symptomatic patients after 6–48 months, improvement of hepatic signs and symptoms was seen with both trientine and penicillamine in 90.9% of treatment-naïve patients and 70.5% of patients who switched treatments. Worsening of hepatic signs and symptoms was seen in only 8/467 patients in the study; 4/204 taking penicillamine first line and 4/45 taking trientine second line, with no significant differences between the groups for line of treatment. There was also no significant difference between the groups in the number of patients who underwent liver transplantation (9/326 patients taking penicillamine and 3/141 patients taking trientine). (See table 3 for more details.) When neurological symptoms were considered, Weiss et al. (2013) found no statistically significant differences in improvements between trientine and penicillamine used first- or second line. In symptomatic patients after 6–48 months, the proportion of patients whose neurological symptoms improved was lower than for hepatic symptoms (first line trientine 55.0% compared with penicillamine 67.5%, second line trientine 51.0% compared with penicillamine 23.1%: differences not statistically significant), with more than a third of patients' symptoms not improving or becoming worse. The number of patients with

worsening of neurological symptoms was statistically significantly similar between the groups in patients who switched treatments. In treatment-naive patients, worsening occurred in statistically significantly more patients in the trientine group (4/20 [20.0%] compared with 6/114 [5.3%] for penicillamine in symptomatic patients,  $p=0.04$ ), although the number of patients taking trientine first line was relatively small.

Taylor et al. (2009) retrospectively studied 16 children with Wilson disease (14 with liver disease) who took trientine. After a median of 6.43 years, liver function became normal in the majority of children. However, 2/3 children taking trientine first line and 4/13 children taking trientine second line still had abnormal liver function. The authors reported that all children who presented with liver symptoms only became symptom-free; however, trientine did not resolve accompanying neurological or psychiatric symptoms in children experiencing these.

The retrospective study by Arnon et al. (2007) evaluated the effects of first line trientine in 10 children with Wilson disease and mixed presentations who were followed up for at least 12 months. Trientine monotherapy was used for 4–8 months before zinc was added (according to urinary copper levels). Alanine aminotransferase (ALT) liver enzyme levels were normal in 3 patients at 12 months and in a further patient after 30 months. In another 3 patients, ALT levels decreased but remained above the upper limit of normal: the authors noted that the clinical significance of a mild increase in liver enzymes is unclear. Similar results were seen for aspartate aminotransferase (AST) levels.

The retrospective study by Walshe (2011) looked at urinary copper excretion and its response to treatment for Wilson disease. In patients with neurological symptoms ( $n=124$ ), 15 patients took trientine (line of treatment unclear) rather than penicillamine. Urinary copper excretion fell over time, approaching the level considered to be normal at 2 years (see table 3 for more details). Similar results were seen with penicillamine. Walshe (2011) suggested that the reduction in copper excretion indicates a reduction in the body load of copper.

### **Safety and tolerability**

In the RCT ( $n=48$ ) comparing tetrathiomolybdate and trientine (Brewer et al. 2006), over 3 years, 1 patient taking trientine had leukopenia (during the 8-week treatment phase) and 4 patients taking trientine died. Three of the patients who died had experienced worsening of neurological symptoms during treatment. No patients stopped treatment or dropped out in the prospective study ( $n=8$ ) investigating once-daily trientine (Ala et al. 2015).

In the retrospective study by Weiss et al. (2013), over a median of 13.3 years, adverse events leading to discontinuation of treatment were more common with penicillamine than with trientine (94/326 [28.8%] compared with 10/141 [7.1%],  $p=0.04$ ). Of these adverse events, arthralgia (29 patients, 8.9%), increase in antinuclear antibodies (22 patients, 6.7%), albuminuria or proteinuria (20 patients, 6.1%) and erythema (11 patients, 3.4%) occurred most commonly with penicillamine. Arthralgia occurred in 4 patients taking trientine (2.8%), 2 patients had nausea or gastric pain (1.4%), and 1 patient (0.7%) experienced each of pruritus, myalgia, nephropathy, leukopenia, increase in antinuclear antibodies,



erythema, lupus erythematosus and hirsutism. No patients died as a result of their treatment.

No significant side effects were seen in the study by Arnon et al. (2007) (n=10). One patient stopped trientine after 12 months because of elevated liver enzyme levels. The dosage of zinc was increased and levels normalised.

In the study by Taylor et al. (2009) (n=16), trientine was discontinued in 3 children who took trientine second line. One had an allergic rash, 1 had low copper excretion and the third required liver transplantation, probably due to non-adherence. After 5.1 years, trientine was restarted in the patient who discontinued trientine because of a rash when his symptoms deteriorated during treatment with zinc, and was well tolerated.

Adverse events were not reported by Askari et al. (2003) or Walshe (2011). According to the Summary of product characteristics for trientine dihydrochloride, nausea has been reported at the start of treatment and, occasionally, skin rash can occur. Duodenitis, severe colitis and, very rarely, anaemia have also been reported.

Trientine has been found to reduce serum iron levels, possibly reducing its absorption. Iron supplementation may be necessary in some cases and should be administered at a different time of the day to trientine (Summary of product characteristics). According to the EASL guideline on managing Wilson disease, zinc should also be administered at a different time of day to trientine to avoid it being chelated.

### **Evidence strengths and limitations**

The studies included in this evidence review are of low quality and have significant limitations that affect their application to clinical practice. The majority are uncontrolled observational studies (generally case series), which are subject to bias and confounding. Two of the observational studies were undertaken prospectively, which may reduce some sources of bias and confounding; 4 were undertaken retrospectively. As is usual for a rare disease, many of the studies had small sample sizes. Surrogate or disease-orientated outcomes (such as liver function or urinary copper excretion) were used in some studies, rather than patient-orientated outcomes (such as hepatic or neurological symptoms). One study was an RCT (Brewer et al. 2006) but it is unclear whether allocation was concealed, outcomes were poorly defined and many patients included in the study had received chelation therapy previously, which had not been controlled for. In addition, zinc was used concomitantly with trientine.

Only Weiss et al. (2013) compared trientine and penicillamine, and this comparison was retrospective. Nevertheless, this study included a large number of patients (n=405) and provides the most useful evidence on using these treatments in people with Wilson disease.

Trientine dihydrochloride (manufactured by Univar) is licensed for treating Wilson disease second line in people who cannot tolerate penicillamine. The definition of penicillamine intolerance is unclear. The EASL guideline on managing Wilson

disease notes that penicillamine is associated with numerous adverse effects and that severe adverse effects require the drug to be discontinued in approximately 30% of patients. (See the Summary of product characteristics for more information, for example, Distamine 250 mg). Taylor et al. (2009) reviewed the literature and found that adverse effects that were reported in studies in which patients were switched from penicillamine to trientine included rash, urticaria, proteinuria, nephrotoxicity, neutropenia, thrombocytopenia and arthritis.

Data from a UK study by Walshe (1982), was used to support the original licence application for trientine for Wilson disease, which was made in 1983 (personal communication Univar, August 2016). The study is a case series that summarises the use of trientine over the previous 13 years in 20 patients with severe penicillamine intolerance (including rash, urticaria, bruising, neutropenia, thrombocytopenia, proteinuria and nephritis) who had taken trientine (1200–2400 mg daily) for more than 1 year. The study found that the adverse effects that forced a change in therapy resolved with trientine in most patients. Eight patients who developed penicillamine intolerance within a week of treatment responded well to trientine treatment, 3 patients who developed intolerance within the first year showed continued improvement, and 9 patients who developed late intolerance remained well controlled. No new adverse effects were seen, although some patients experienced iron deficiency, which was corrected with iron supplements.

Some of the studies included in the evidence summary used trientine first line in newly diagnosed patients, which would be off-label in the UK. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using trientine first line outside its authorised indications.

There is more clinical experience of using penicillamine, rather than trientine first line. In the study by Weiss et al. (2013), only 36 people took trientine first line compared with 294 people who took penicillamine first line. By contrast, 105 people took trientine second line compared with 32 who used penicillamine second line (some people took more than 1 treatment).

Many of the studies used a 250 mg formulation of trientine. It is unclear how the bioavailability of this formulation compares with the 300 mg formulation that is licensed in the UK, and whether the effects of treatment would be the same. Dosage regimens differed in the studies or were not reported.

Some of the studies used trientine plus zinc, whereas some used trientine alone. It is unclear whether the combination has any advantages or disadvantages over monotherapy in terms of safety or efficacy. Compliance with treatment is likely to be an issue with combination therapy because the treatments cannot be taken at the same time. In some of the studies, trientine was stopped after a period of time and zinc was used alone for maintenance therapy.

- Better quality studies are needed to compare the safety and efficacy of trientine, penicillamine and zinc, and clarify their places in therapy. It is difficult to perform high quality RCTs with large sample sizes in rare diseases, although multicentre RCTs may be an option. An observational study is

currently underway, in which 90 patients with Wilson disease who changed treatment from penicillamine to trientine are being reviewed retrospectively for 48 months and followed prospectively for a further 12 months (NCT02426905). Results are expected to be available in 2018 (personal communication Univar, July 2016).

Trientine should be stored in a refrigerator in the original container with the silica gel sachet. The EASL guideline on managing Wilson disease advises that it should be administered 1 hour before or 3 hours after meals, but that taking it closer to meals is acceptable if this ensures compliance. Penicillamine and zinc 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).

## 6. Conclusion

Efficacy, safety, cost and patient factors should be into account when considering the place in therapy of trientine.

There is a lack of high quality evidence to estimate the relative treatment effects of the available drugs for treating Wilson disease (EASL guideline on managing Wilson disease). From the largest observational study (Weiss et al. 2013), trientine was as effective as penicillamine for reducing hepatic and neurological signs and symptoms when used first or second line. Hepatic signs and symptoms were reduced in 90.9% of symptomatic patients taking first line therapy and 70.5% of symptomatic patients taking second line therapy with either drug. The proportion of patients experiencing improvement in neurological symptoms was lower, with more than a third of patients not improving or becoming worse in both treatment groups. Weiss et al. (2013) suggested that cerebral damage caused by copper toxicity may be at least partly irreversible.

Some limited evidence supports the use of trientine plus zinc to reduce hepatic and neurological signs and symptoms in newly diagnosed patients (Brewer et al. 2006 and Askari et al. 2003) However, it is unclear whether the combination has any benefits over trientine monotherapy.

Trientine was generally well tolerated in the studies. In the study by Weiss et al. (2013), statistically significantly more patients discontinued treatment because of adverse events with penicillamine compared with trientine (28.8% compared with 7.1%,  $p=0.04$ ). Guidelines from the EASL and the AASLD recommend either penicillamine or trientine for treating Wilson disease, but note that trientine may be better tolerated.

## 7. Evidence Summary Tables

| Use of tetrathiomolybdate (an experimental chelating agent which is not currently available) compared with trientine dihydrochloride for Wilson disease |   |   |  |                                       |  |  |                           |               |  |
|---|---|---|--|---------------------------------------|--|--|---------------------------|---------------|--|
| Study reference   | Study Design  | Population characteristics  | Intervention   | Outcome measure type                  | Outcome measures   | Results  | Quality of Evidence Score | Applicability | Critical Appraisal Summary   |
| Brewer et al. 2006  | P1<br>Randomised, double blind controlled study comparing tetrathiomolybdate and trientine in patients with neurological symptoms of Wilson disease. General Clinical Research Center of the University of Michigan Hospital. | 48 primarily newly diagnosed patients with neurological symptoms of Wilson disease were included. Patients who had received penicillamine or trientine for more than 28 days were excluded. Some included patients had stopped penicillamine more than a year ago and later developed new neurological symptoms. Mean age was 28 years (range 13–49 years). 30/48 patients were male. | Patients were randomised to receive tetrathiomolybdate 20 mg 6 times daily or trientine 500 mg twice daily (plus matching placebo) for 8 weeks. All patients received zinc 50 mg twice daily, which they continued on discharge from the hospital. Baseline characteristics appeared broadly similar between the groups.<br><br>Follow up was 3 years. | Primary<br><br>Clinical effectiveness | Neurological deterioration - defined as an increase of 5 points on a quantitative neurological examination scale (range 0–38). | 6/23 patients in the trientine group and 1/25 patients in the tetrathiomolybdate group experienced neurological deterioration. The difference between the groups was statistically significant ( $p < 0.05$ ). | 6                         | Direct        | <ul style="list-style-type: none"> <li>Unclear whether allocation was concealed</li> <li>Outcomes were poorly defined</li> <li>Many patients included in the study had received chelation therapy previously, which had not been controlled for.</li> <li>Zinc was used concomitantly with trientine.</li> <li>Short follow up period</li> <li>Surrogate outcomes</li> </ul> |
|   |   |   |  | Primary<br><br>Clinical effectiveness | Speech deterioration - was defined as an increase of 3 points on a speech examination scale (range 0–7).                       | No patients in either group met the criteria for speech deterioration.   |                           |               |  |
|   |   |   |  | Secondary<br><br>Safety               | Adverse events   | Over 8 weeks, 1 person in the trientine group had leukopenia. 4 patients taking trientine died during follow up.   |                           |               |  |

| Use of trientine dihydrochloride plus zinc for Wilson disease |   |  |  |                        |   |   |                           |               |   |
|---|---|--|--|------------------------|---|---|---------------------------|---------------|---|
| Study reference   | Study Design  | Population characteristics   | Intervention   | Outcome measure type   | Outcome measures  | Results   | Quality of Evidence Score | Applicability | Critical Appraisal Summary  |
| Askari et al. 2003  | P1<br><br>Study of trientine plus zinc in patients newly diagnosed with liver failure caused by Wilson disease. General Clinical Research Center of the University of Michigan Hospital | This study included 9 patients with hepatic decompensation (Serum albumin less than 2.8 g/dL and prothrombin time prolonged by over 2.5 seconds. 8 patients also had hyperbilirubinaemia and 7 had ascites) who were potential candidates for liver transplantation based on their CTP scores (range 9–13). Patients with neurological symptoms were excluded, as were those who had been treated with another therapy for more than a month.<br><br>Mean age was 25 years (range 19–32 years). 6/9 patients were female | Trientine 1,000 mg/day and zinc 150 mg/day were taken for at least 4 months (initial 6–8 weeks in hospital).<br><br>After 2 weeks, 1 patient with mild neurological symptoms was transferred to another clinical trial and randomised to receive tetrathiomolybdate 120 mg/day plus zinc 50 mg/day for 8 weeks then zinc alone.<br><br>Mean follow up was 6.2 years (range 12 months to 14 years). | Primary                | Liver function tests – Albumin, prothrombin time and bilirubin levels | Within 12 months, in all patients, albumin levels, prolonged prothrombin time and bilirubin levels became normal. Ascites, fatigue, nausea and vomiting resolved with treatment. Benefits persisted in all patients during follow up. | 4                         | Direct        | <ul style="list-style-type: none"> <li>• Small sample</li> <li>• Uncontrolled observational study</li> <li>• Surrogate outcomes</li> <li>• Needle biopsies sample only a tiny portion of a large organ</li> </ul> |
|   |   |  |  | Clinical effectiveness |   |   |                           |               |   |

| Use of trientine dihydrochloride plus zinc for Wilson disease |   |  |   |                                       |                  |   |                           |               |   |
|---|---|--|---|---------------------------------------|------------------|---|---------------------------|---------------|---|
| Study reference   | Study Design  | Population characteristics   | Intervention  | Outcome measure type                  | Outcome measures | Results   | Quality of Evidence Score | Applicability | Critical Appraisal Summary  |
| Amon et al. 2007  | P1<br>Case review of the records of children with Wilson disease to evaluate the efficacy of and adherence to trientine and/or zinc.<br>Mount Sinai School of Medicine, New York. | 10 children who were evaluated and treated between 1998 and 2006 received first line trientine and were followed up for at least 12 months. Presentation was recorded as incidental in 5 patients, hepatic in 2 patients, mixed hepatic/neurological in 1 patient, neuropsychiatric in 1 patient and via screening in 1 patient. The median age at diagnosis was about 12 years (range 8–17 years). 8/10 patients were male. | Initial therapy was trientine 250–500 mg twice daily. After around 4–8 months zinc 25–50 mg twice daily was added (was added once evidence of chelation was seen -urinary copper levels below 200 micrograms/24 hours). All patients took zinc monotherapy by 18 months. Trientine was stopped when urinary copper levels were 60–200 micrograms/24 hours).<br><br>Follow up was 12–60 months | Primary<br><br>Clinical effectiveness | ALT levels       | ALT levels were normal in 3 patients within 12 months and in a further patient after 30 months. In 3 patients, ALT levels decreased but remained above the upper limit of normal. Mean ALT levels decreased from 183 units/litre at baseline to 80 units/litre at 12 months (n=10) and 66 units/litre at 18 months (n=7). Similar results were seen for AST levels. | 3                         | Direct        | <ul style="list-style-type: none"> <li>• Small sample</li> <li>• Uncontrolled observational study</li> <li>• Patients with mixed presentations</li> <li>• Trientine monotherapy was used for 4–8 months before zinc was added followed by stopping of trientine once copper levels were reached.</li> </ul> |
|   |   |  |   | Primary<br><br>Clinical effectiveness | Adherence        | Non-adherence was identified in 4 patients by increased ALT levels and low urinary levels of zinc, including 1 patient whose ALT had previously become normal.  |                           |               |   |
|   |   |  |   | Secondary<br><br>Safety               | Side-effects     | No significant side effects were seen. 1 patient stopped trientine after 12 months because of elevated liver enzyme levels.   |                           |               |   |

| Use of trientine dihydrochloride alone for Wilson disease |   |  |   |   |  |   |                           |               |  |
|---|---|--|---|---|--|---|---------------------------|---------------|--|
| Study reference   | Study Design  | Population characteristics   | Intervention  | Outcome measure type                    | Outcome measures   | Results   | Quality of Evidence Score | Applicability | Critical Appraisal Summary   |
| Ala et al. 2015   | P1<br>Pilot study of a single daily dose of trientine for Wilson disease. Yale University Medical Center. | This study included 8 patients who had been stable on current treatment (5 trientine, 2 zinc and 1 penicillamine) for over 1 year (median 8 years, range 3–50 years), with stable liver disease.<br><br>Age ranged from 22–71 years. 7/8 patients were male. | Trientine 15 mg/kg (rounded upwards to the nearest 250 mg) was taken once daily for 12 months.  | Primary<br><br>Clinical effectiveness   | Neurological signs   | Physical examination remained unchanged and no new neurological signs were detected.  | 4                         | Direct        | <ul style="list-style-type: none"> <li>• Small sample with stable disease</li> <li>• Uncontrolled observational study</li> <li>• Short follow up period</li> </ul> |
|   |   |  |   | Primary<br><br>Clinical effectiveness   | Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels | Laboratory test results were generally stable, although ALT and AST (liver enzymes) increased in some patients, none of whom required treatment to be stopped.  |                           |               |  |
|   |   |  |   | Secondary<br><br>Clinical effectiveness | Adherence  | Patients' questionnaires revealed once-daily trientine was easier to adhere to and preferable to having to time treatment around meals.   |                           |               |  |
| Taylor et al. 2009  | P1<br>Case review of the medical notes of children taking trientine for Wilson disease.                   | 16/96 children diagnosed between 1981 and 2006 took trientine: 3 first line (parental choice in 2 cases, 1 case had an allergic reaction to penicillamine during a challenge test) and 13 second line following  | The initial dosage of trientine was 600 mg/day in children aged less than 12 years and 1200 mg/day in children aged over 12 years, increasing to 1500 mg/day or 2400 mg/day. Median follow up | Primary<br><br>Clinical effectiveness   | Liver function   | 2/3 children taking trientine first line and 4/13 children taking trientine second line still had abnormal liver function during trientine treatment. Nevertheless, all children who presented with liver symptoms only reportedly became symptom-free. | 3                         | Direct        | <ul style="list-style-type: none"> <li>• Small sample</li> <li>• Uncontrolled observational study</li> </ul>   |

| Use of trientine dihydrochloride alone for Wilson disease |                                  |   |   |                      |                  |         |                           |               |                            |
|---|----------------------------------|---|---|----------------------|------------------|---------|---------------------------|---------------|----------------------------|
| Study reference   | Study Design                     | Population characteristics  | Intervention                            | Outcome measure type | Outcome measures | Results | Quality of Evidence Score | Applicability | Critical Appraisal Summary |
|   | King's College Hospital, London. | <p>adverse reactions to penicillamine (including haematuria, bone marrow suppression and neutropenia) after a median of 0.84 years.</p> <p>On admission, 2 children had acute liver failure, 12 had chronic liver disease and 2 were diagnosed via family screening. Neurological symptoms or psychiatric symptoms were seen in 3 children. Median age was 10.5 years (range 6.6–15 years). 11/16 patients were male.</p> | was 6.43 years (range 0.78–18.6 years). |                      |                  |         |                           |               |                            |



| Use of trientine dihydrochloride alone for Wilson disease |              |                            |              |                                   |                                      |   |                           |               |                            |
|---|--------------|----------------------------|--------------|-----------------------------------|--------------------------------------|---|---------------------------|---------------|----------------------------|
| Study reference   | Study Design | Population characteristics | Intervention | Outcome measure type              | Outcome measures                     | Results   | Quality of Evidence Score | Applicability | Critical Appraisal Summary |
|   |              |                            |              | Primary<br>Clinical effectiveness | Neurological or psychiatric symptoms | Trientine did not resolve accompanying neurological or psychiatric symptoms.  |                           |               |                            |
|   |              |                            |              | Secondary<br>Safety               | Safety                               | Trientine was discontinued in 3 children who took trientine second line. 1 had an allergic rash, 1 had low copper excretion and the third required liver transplantation. |                           |               |                            |

| Use of trientine dihydrochloride alone for Wilson disease |   |   |   |                                       |                  |   |                           |               |  |
|---|---|---|---|---------------------------------------|------------------|---|---------------------------|---------------|--|
| Study reference   | Study Design  | Population characteristics  | Intervention  | Outcome measure type                  | Outcome measures | Results   | Quality of Evidence Score | Applicability | Critical Appraisal Summary   |
| Walsh e 2011  | Case review to find out if urinary copper excretion shows a response to treatment for Wilson disease. Middlesex Hospital, London. | 192 cases seen between 1955 and 2000 included sufficient information. Patients were excluded if they were seen before best practice was established, were referred too late after diagnosis, or appeared to have inaccurate urinary copper readings. Patients were divided into groups of pre-symptomatic (n=31), hepatic (n=37) and neurological (n=124) Wilson disease at diagnosis. The median age of the neurological group was 20 years (range 7–39 years). Gender was not reported. | 15/124 patients in the neurological group took trientine rather than penicillamine for 2 years. No patients in the other groups took trientine. | Primary<br><br>Clinical effectiveness | Copper excretion | At 1 year, basal copper excretion had fallen from 193 micrograms/24 hours to 53 micrograms/24 hours. At 2 years, it fell further to 38 micrograms/24 hours, approaching the normal level of 30 micrograms/24 hours. Similar results were seen in the other groups and with penicillamine. Progress of clinical symptoms was not reported. | 3                         | Direct        | <ul style="list-style-type: none"> <li>• Small sample</li> <li>• Uncontrolled observational study</li> <li>• It is not reported if trientine was first- or second line.</li> <li>• Uncontrolled observational study</li> </ul> |

| Use of trientine dihydrochloride alone for Wilson disease |  |   |  |                                       |                       |   |                           |               |   |
|---|--|---|--|---------------------------------------|-----------------------|---|---------------------------|---------------|---|
| Study reference   | Study Design   | Population characteristics  | Intervention   | Outcome measure type                  | Outcome measures      | Results   | Quality of Evidence Score | Applicability | Critical Appraisal Summary  |
| Weiss et al. 2013   | P1<br>Case review of patients with Wilson disease treated with chelating agents in tertiary care centres in Germany and Austria and the EUROWILSON registry. | 380 patients from 3 tertiary care centres in each of Germany and Austria, plus 25 patients from the EUROWILSON registry were included (n=405). Patients were categorised according to symptoms at diagnosis: asymptomatic (n=54), hepatic (n=207) neurological (n=92) or mixed hepatic and neurological (n=52). 21 patients had liver failure at diagnosis. The median age at diagnosis was about 18 years. 238/405 patients were female. | Data were analysed for penicillamine (n=326) and trientine (n=141) monotherapy (total n=467 because some patients received more than one treatment). Zinc monotherapy and combination therapy were not analysed. Treatment blocks with less than 6 months' follow were excluded. Baseline characteristics were generally similar between the treatment groups. Hepatic, e and neurological, e outcomes were assessed at 6, 12, 24, 36 and 48 months after initiation of the current treatment regimen and stratified according to first- (n=294 for penicillamine and n=36 for trientine) or second line (n=32 and n=105 respectively) use. Median follow up was 13.3 years up | Primary<br><br>Clinical effectiveness | Hepatic outcomes      | 9/326 (2.8%) patients taking penicillamine and 3/141 (2.1%) patients taking trientine underwent liver transplantation (no significant difference).<br><br>In asymptomatic and symptomatic patients, worsening of hepatic outcomes was seen in 4/295 (1.4%) taking penicillamine first line and 4/103 (3.9%) taking trientine second line with no worsening seen with first line trientine or second line penicillamine. There were no significant differences between the groups for either line of treatment (p=1 and p=0.6 respectively). | 3                         | Direct        | <ul style="list-style-type: none"> <li>Uncontrolled observational studies</li> <li>Patients with mixed presentations</li> </ul> |
|   |  |   |  | Primary<br><br>Clinical effectiveness | Neurological outcomes | In symptomatic neurological patients, no statistically significant differences were seen between the groups in rates of improvement for first- (77/114 [67.5%] for penicillamine compared with 11/20 [55.0%] for trientine, p=0.3) or second line treatment (3/13 [23.1%] compared with 26/51 [51.0%] respectively, p=0.1).<br><br>In asymptomatic and symptomatic patients, worsening of neurological outcomes was not statistically significantly different between   |                           |               |   |

| Use of trientine dihydrochloride alone for Wilson disease |              |                            |              |                      |                  |  |                           |               |                            |
|---|--------------|----------------------------|--------------|----------------------|------------------|--|---------------------------|---------------|----------------------------|
| Study reference   | Study Design | Population characteristics | Intervention | Outcome measure type | Outcome measures | Results  | Quality of Evidence Score | Applicability | Critical Appraisal Summary |
|   |              |                            |              |                      |                  | the groups for second line treatment (1/31 [3.4%] with penicillamine compared with 8/103 [7.8%] with trientine, p=0.7). However, a statistically significant difference was seen for first line treatment, with more worsening seen with trientine (4/38 [10.5%] compared with 6/295 [2.0%] with penicillamine, p=0.02). |                           |               |                            |
|   |              |                            |              | Secondary            | Safety           | Discontinuation due to adverse events was seen in 94/326 patients (28.8%) on penicillamine compared with 10/141 patients (7.1%) taking trientine (p=0.04). No deaths related to adverse events were seen.  |                           |               |                            |
|   |              |                            |              | Safety               |                  |  |                           |               |                            |

## 8. Grade of evidence tables

| Use of tetrathiomolybdate (an experimental chelating agent which is not currently available) compared with trientine dihydrochloride for Wilson disease |                    |                           |               |                   |  |
|---|--------------------|---------------------------|---------------|-------------------|--|
| Outcome Measure   | Reference          | Quality of Evidence Score | Applicability | Grade of Evidence | Interpretation of Evidence   |
| Neurological deterioration  | Brewer et al. 2006 | 6                         | Direct        | C                 | Neurological deterioration was defined as an increase of 5 points on a quantitative neurological examination scale (range 0–38).<br><br>In a study with 48 patient randomised to receive tetrathiomolybdate or trientine for 8 weeks, 6/23 patients in the trientine |

| Use of tetrathiomolybdate (an experimental chelating agent which is not currently available) compared with trientine dihydrochloride for Wilson disease |                    |                           |               |                   |  |
|---|--------------------|---------------------------|---------------|-------------------|--|
| Outcome Measure   | Reference          | Quality of Evidence Score | Applicability | Grade of Evidence | Interpretation of Evidence   |
|   |                    |                           |               |                   | group and 1/25 patients in the tetrathiomolybdate group experienced neurological deterioration. The difference between the groups was statistically significant ( $p < 0.05$ ).  |
| Speech deterioration  | Brewer et al. 2006 | 6                         | Direct        | C                 | Speech deterioration was defined as an increase of 3 points on a speech examination scale (range 0–7).<br><br>In a study with 48 patient randomised to receive tetrathiomolybdate or trientine for 8 weeks, no patients in either group met the criteria for speech deterioration. |
| Adverse events  | Brewer et al. 2006 | 6                         | Direct        | C                 | In a study with 48 patient randomised to receive tetrathiomolybdate or trientine for 8 weeks, 1 person in the trientine group had leukopenia. 4 patients taking trientine died during follow up.   |

| Use of trientine dihydrochloride plus zinc for Wilson disease |                    |                           |               |                   |   |
|---|--------------------|---------------------------|---------------|-------------------|---|
| Outcome Measure   | Reference          | Quality of Evidence Score | Applicability | Grade of Evidence | Interpretation of Evidence  |
| Liver function  | Askari et al. 2003 | 4                         | Direct        | C                 | This study included 9 patients with hepatic decompensation (Serum albumin less than 2.8 g/dL and prothrombin time prolonged by over 2.5 seconds). Within 12 months, in all patients treated for at least 4 months, albumin levels, prolonged prothrombin time and bilirubin levels became normal. Ascites, fatigue, nausea and vomiting resolved with treatment. Benefits persisted in all patients during follow up. |
|   | Amon et al. 2007   | 3                         | Direct        |                   |   |
| Hepatic fibrosis  | Askari et al. 2003 | 4                         | Direct        | C                 | This study included 9 patients with hepatic decompensation (Serum albumin less than 2.8 g/dL and prothrombin time prolonged by over 2.5 seconds). Patients were treat for   |

| Use of trientine dihydrochloride plus zinc for Wilson disease |                  |                           |               |                   |  |
|---|------------------|---------------------------|---------------|-------------------|--|
| Outcome Measure   | Reference        | Quality of Evidence Score | Applicability | Grade of Evidence | Interpretation of Evidence   |
|   |                  |                           |               |                   | <p>at least 4 months.</p> <p>Hepatic fibrosis was reduced in 3 patients who had serial liver biopsies. After 6 months, no patients met the criteria for liver transplantation (Child-Turcotte-Pugh score became 5 in all patients).</p> <p>CTP score is used for assessing the severity of cirrhosis and need for liver transplantation, a score of 8 is the minimum for a liver transplant.</p> |
| Adherence   | Amon et al. 2007 | 3                         | Direct        | C                 | <p>In a study, 10 children who were evaluated and treated (Trientine monotherapy was used for 4–8 months before zinc was added followed by stopping of trientine once copper levels were reached).</p> <p>Non-adherence was identified in 4 patients by increased ALT levels and low urinary levels of zinc, including 1 patient whose ALT had previously become normal.</p>                     |
| Side-effects  | Amon et al. 2007 | 3                         | Direct        | C                 | <p>In a study, 10 children who were evaluated and treated (Trientine monotherapy was used for 4–8 months before zinc was added followed by stopping of trientine once copper levels were reached).</p> <p>No significant side effects were seen. 1 patient stopped trientine after 12 months because of elevated liver enzyme levels.</p>  |

| Use of trientine dihydrochloride alone for Wilson disease |                    |                           |               |                   |  |
|---|--------------------|---------------------------|---------------|-------------------|--|
| Outcome Measure   | Reference          | Quality of Evidence Score | Applicability | Grade of Evidence | Interpretation of Evidence   |
| Neurological signs  | Ala et al. 2015    | 4                         | Direct        | C                 | A study included 8 patients who had been stable on current treatment (5 trientine, 2 zinc and 1 penicillamine) for over 1 year (median 8 years, range 3–50 years), with stable liver disease. It reported that physical examination remained unchanged and no new neurological signs were detected.  |
|   | Taylor et al. 2009 | 3                         | Direct        |                   |  |
|   | Weiss et al. 2013  | 3                         | Direct        |                   |  |
| Liverfunction   | Ala et al. 2015    | 4                         | Direct        | C                 | A study included 8 patients who had been stable on current treatment (5 trientine, 2 zinc and 1 penicillamine) for over 1 year (median 8 years, range 3–50 years), with stable liver disease.<br><br>Laboratory test results were generally stable in patients, although ALT and AST (liver enzymes) increased in some patients, none of whom required treatment to be stopped.  |
|   | Taylor et al. 2009 | 3                         | Direct        |                   |  |
|   | Taylor et al. 2009 | 3                         | Direct        |                   |  |
| Hepatic outcomes  | Weiss et al. 2013  | 3                         | Direct        | C                 | In a study, data were analysed for penicillamine (n=326) and trientine (n=141).<br><br>9/326 (2.8%) patients taking penicillamine and 3/141 (2.1%) patients taking trientine underwent liver transplantation (no significant difference).<br><br>In asymptomatic and symptomatic patients, worsening of hepatic outcomes was seen in 4/295 (1.4%) taking penicillamine first line and 4/103 (3.9%) taking trientine second line with no worsening seen with first line trientine or second line penicillamine. There were no significant differences between the groups for either line of treatment (p=1 and p=0.6 respectively). |
| Copper excretion  | Walsh 2011         | 3                         | Direct        | C                 | In a study, 15 patients with neurological (n=124) Wilson disease at diagnosis were treated with trientine monotherapy.   |

|           |                    |   |        |   |   |
|-----------|--------------------|---|--------|---|---|
|           |                    |   |        |   | At 1 year, basal copper excretion had fallen from 193 micrograms/24 hours to 53 micrograms/24 hours. At 2 years, it fell further to 38 micrograms/24 hours, approaching the normal level of 30 micrograms/24 hours. Similar results were seen in the other groups and with penicillamine. Progress of clinical symptoms was not reported. |
| Adherence | Ala et al. 2015    | 4 | Direct | C | A study included 8 patients who had been stable on current treatment (5 trientine, 2 zinc and 1 penicillamine) for over 1 year.<br><br>Patients' questionnaires revealed once-daily trientine was easier to adhere to and preferable to having to time treatment around meals.  |
| Safety    | Taylor et al. 2009 | 3 | Direct | C | In a study with 16 patients of whom 3 took trientine first line and remaining second line. Trientine was discontinued in 3 children who took trientine second line. 1 had an allergic rash, 1 had low copper excretion and the third required liver transplantation   |

## 9. Literature Search Terms

| <b>Search strategy</b> <i>Indicate all terms to be used in the search</i>   |  |
|---|--|
| <b>P – Patients/ Population</b><br><br>Which patients or populations of patients are we interested in?<br>How can they be best described? Are there subgroups that need to be considered? |  |
| <b>I – Intervention</b><br><br>Which intervention, treatment or approach should be used?  |  |





## 12. References

- Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson disease. *Lancet*. 2007;369:397–408
- Ala A, Aliu E and Schilsky ML (2015) Prospective pilot study of a single daily dosage of trientine for the treatment of Wilson disease. *Digestive Diseases and Sciences* 60: 1433–9
- Arnon R, Calderon JF, Schilsky M et al. (2007) Wilson disease in children: serum aminotransferases and urinary copper on triethylene tetramine dihydrochloride (trientine) treatment. *Journal of Pediatric Gastroenterology and Nutrition* 44: 596–602.
- Askari FK, Greenson J, Dick RD et al. (2003) Treatment of Wilson disease with zinc. XVIII. Initial treatment of the hepatic decompensation presentation with trientine and zinc. *Journal of Laboratory and Clinical Medicine* 142: 385–90
- Brewer GJ, Askari F, Lorincz MT et al. (2006) Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. *Archives of Neurology* 63: 521–7
- Rodriguez-Castro KI, Hevia-Urrutia FJ, Sturniolo GC. Wilson disease: A review of what we have learned. *World J Hepatol*. 2015 Dec 18. 7 (29):2859-70
- Taly AB, Meenakshi-Sundaram S, Sinha S, Swamy HS, Arunodaya GR. Wilson disease: description of 282 patients evaluated over 3 decades. *Medicine (Baltimore)* 2007;86:112–21.
- Taylor RM, Chen Y, Dhawan A on behalf of the EUROWILSON Consortium (2009) Triethylene tetramine dihydrochloride (trientine) in children with Wilson disease: experience at King's College Hospital and review of the literature. *European Journal of Pediatrics* 168:1061–8
- Purchase R; The treatment of Wilson disease, a rare genetic disorder of copper metabolism. *Sci Prog*. 2013;96(Pt 1):19-32
- Walshe JM (2011) The pattern of urinary copper excretion and its response to treatment in patients with Wilson disease. *QJM* 104: 775–8
- Weiss KH, Thurik F, Gotthardt DN et al. (2013) Efficacy and safety of oral chelators in treatment of patients with Wilson disease. *Clinical Gastroenterology and Hepatology* 11: 1028–35

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