Received: 13 February 2019 | Revised: 16 May 2019 | Accepted: 4 June 2019

DOI: 10.1111/liv.14179

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Comparative effectiveness of common therapies for Wilson disease: A systematic review and meta-analysis of controlled studies

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Funding information
There was no specific external funding supporting this work.

Handling Editor: Janus Ong

Abstract

Background & aims: Wilson disease (WD) is a rare disorder of copper metabolism. The objective of this systematic review was to determine the comparative effectiveness and safety of common treatments of WD.

Methods: We included WD patients of any age or stage and the study drugs D-penicillamine, zinc salts, trientine and tetrathiomolybdate. The control could be placebo, no treatment or any other treatment. We included prospective, retrospective, randomized and non-randomized studies. We searched Medline and Embase via Ovid, the Cochrane Central Register of Controlled Trials, and screened reference lists of included articles. Where possible, we applied random-effects meta-analyses.

Results: The 23 included studies reported on 2055 patients and mostly compared D-penicillamine to no treatment, zinc, trientine or succimer. One study compared tetrathiomolybdate and trientine. Post-decoppering maintenance therapy was addressed in one study only. Eleven of 23 studies were of low quality. When compared to no treatment, D-penicillamine was associated with a lower mortality (odds ratio 0.013; 95% CI 0.0010 to 0.17). When compared to zinc, there was no association with mortality (odds ratio 0.73; 95% CI 0.16 to 3.40) and prevention or amelioration of clinical symptoms (odds ratio 0.84; 95% CI 0.48 to 1.48). Conversely, D-penicillamine may have a greater impact on side effects and treatment discontinuations than zinc.

Conclusions: There are some indications that zinc is safer than D-penicillamine therapy while being similarly effective in preventing or reducing hepatic or neurological WD symptoms. Study quality was low warranting cautious interpretation of our findings.

KEYWORDS
hepatolenticular degeneration, meta-analysis, systematic review, Wilson disease

1 | INTRODUCTION

Wilson disease (WD), also known as hepatolenticular degeneration, is an autosomal recessively inherited disorder of copper metabolism.[1,2] It is caused by mutations in *ATP7B*, which encodes a copper transporting ATPase that is expressed in the liver.[3] ATP7B-mediated copper translocation is essential for the excretion of copper into the bile. Defective ATP7B function will therefore result in a gradually increasing copper concentration in the liver, which ultimately exceeds natural buffering capacity.[1] At that point, patients may develop acute liver failure, sometimes

Abbreviations: CI, confidence interval; DPen, D-penicillamine; NOS, Newcastle-Ottawa scale; OLT, orthotopic liver transplantation; OR, odds ratio; TTM, tetrathiomolybdate; WD, Wilson disease; Zn, zinc salts.

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accompanied with haemolytic anaemia, because of the release of unbound copper from the liver into the circulation.[4] In other patients, liver disease develops more gradually. Copper will also disseminate to other organs, most notably the brain, where it causes a characteristic movement disorder.[5] This is because of copper deposition in the basal ganglia, which are most severely affected, but a range of other neurological and/or psychological symptoms may also develop in response to copper overload.[5]

None of the available medical treatments for WD can cure the disease and all require a life-long oral regimen. They aim at reducing copper overload in the body, either by the copper chelators D-penicillamine (DPen)[6] or trientine,[7] which immediately increase urinary copper excretion, or by zinc salts (Zn),[8,9] which inhibit intestinal copper absorption through slow transcriptional induction of cellular metallothioneins.[10] After a lag phase, Zn also induces net excretion of copper from the body.[11] Another important, emerging treatment is tetrathiomolybdate (TTM) which binds excess copper and promotes biliary copper excretion.[12] Contrary to DPen and trientine, it not only captures free plasma copper but also seems to have an additional protective activity component within cells.[13] As it was too unstable for routine application in its original formulation as ammonium salt, it was never used widely. This may, however, change since a stable bis-choline salt has been developed and implemented recently.[14,15] Irrespective of the drug used, the therapy of WD can be divided into an initial de-coppering phase with a negative copper balance and a subsequent maintenance phase where intake and excretion of copper roughly balance each other.[1] Likewise, all of the copper-lowering drugs strongly require good compliance with treatment to be successful.[16]

The choice between a chelator and Zn for the treatment of copper overload in patients with WD is not straightforward. Owing to the low incidence and heterogeneous symptomatology of WD,[1] the design and realization of clinical trials that compare the effectiveness of available treatment options is extraordinarily challenging. Thus, clinical decisions often rely more on the patient's or physician's preference or drug availability than on evidence. Probably mostly owing to the fact that DPen was introduced as a successful treatment for WD in the late 1950s – at least 30 years before any other treatment used today[6] – it has remained the standard of care for WD patients in most countries.[17] The dominance of DPen or, more generally, chelator therapy is also reflected in current guidelines.[18-21] These suggest that symptomatic patients should be treated with a chelating agent, although Zn may be used as first-line therapy in those with neurological disease.[18-21] In presymptomatic patients, either a chelator or Zn can be used.[18-21] These recommendations were partly based on a systematic review on initial treatment of WD from 2009 that included all studies published at that time describing outcome, both controlled and non-controlled.[22] This systematic review was limited by the small number of symptomatic patients that were treated with Zn. Still, it suggested that severe side effects necessitating drug withdrawal were more frequent on DPen than on Zn.[22] Also, neurological deterioration after the start of decoppering therapy appeared to occur more frequently when using DPen as compared to Zn.[22]

Keypoints

- This systematic review compared effectiveness and safety of D-penicillamine, zinc, trientine, and tetrathiomolybdate for initial or maintenance treatment of Wilson disease.
- No difference in effectiveness could be detected between D-penicillamine and zinc.
- Zinc may be safer than D-penicillamine.
- Only few data on other drug comparisons and on the maintenance phase of treatment were found.
- The certainty of evidence was low due to a lack of randomized controlled clinical data.

As a number of new studies that compared different treatments of WD have been published since 2009, we now performed a systematic review focusing on controlled studies only. The aim of this systematic review was to assess the comparative effectiveness of common WD therapies on patient-relevant outcomes.

2 | MATERIALS AND METHODS

2.1 | Eligibility criteria

We included WD patients of any age or stage. The study drug had to be one of four established therapies, namely DPen, trientine, TTM or Zn. The control could be placebo, no treatment or any other treatment that does not include the respective study drug (eg Zn vs trientine was allowed, Zn 50 mg vs Zn 100 mg was not allowed). Concomitant therapies had to be identical in the compared treatment arms (eg trientine plus Zn vs TTM plus Zn). Comparisons between monotherapy and combination therapy regimens that included the respective monotherapy drug (eg DPen plus Zn vs Zn) have been analysed elsewhere[23] and were not considered any further here. We included studies that reported all-cause mortality, orthotopic liver transplantation (OLT), neurological symptoms (eg dystonia, dysarthria, cognitive decline, drooling, tremor, gait disturbance, chorea, seizure, psychosis), liver-related symptoms (eg icterus, ascites, steatosis, fibrosis, mild hepatitis, acute liver failure, cirrhosis, serum transaminases), adverse effects (eg dermatological manifestations, nephrotoxicity, pulmonary toxicity, autoimmune disorders, anaemia, neutrophilic agranulocytosis, thrombocytopenia, hypothyroidism, liver dysfunction, colitis, status dystonicus, myasthenia gravis, arthropathy, macromastia, early neurological deterioration, gastrointestinal irritation), and frequency of treatment discontinuation (ie switching to another drug, stopping or changing the treatment). We included prospective and retrospective studies, including randomized, non-randomized controlled trials and comparative observational studies that were written in English, German, Dutch, French, Spanish or Portuguese. Animal studies, case reports, case series, cross-sectional studies, before-after studies, reviews, letters, abstract-only publications, editorials, diagnostic or other testing

studies and non-controlled studies were excluded. No publication date restrictions were applied.

2.2 | Identification of relevant literature

2.2.1 | Electronic searches

Two information specialists (CA-H, HE) developed the search strategy. Text words (synonyms and word variations) and database-specific subject headings for WD, DPen, trientine, Zn and TTM were used. We searched the electronic databases Medline and Embase via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) (last search 31 January 2019) (Appendix S1). All retrieved references were exported to Endnote X8 and deduplicated.

2.2.2 | Searching other resources

To identify possible additional studies that escaped our electronic database searches, we screened the reference lists of the full-text papers of all included articles and of key systematic reviews (backward citation chasing).[24] For this purpose, we retrieved systematic reviews during title abstract screening that had a similar research question as we do, and that were described as 'systematic (literature) review' (semantic variations allowed) or that described a systematic literature search in their methods section. [22,23,25-31]

2.3 | Data collection and analysis

2.3.1 | Study selection

Two reviewers (HE, CA-H) independently pilot-screened the first 200 references, the rest were screened by one reviewer (CA-H). Any uncertainties were solved by discussion (HE, CA-H). All potentially relevant references were retrieved in full-text and independently assessed by two reviewers (CA-H, RHJH). Any disagreements over eligibility were resolved by consensus. Where necessary, a third review author (HE) made a final judgement. We recorded the selection process and the reasons for exclusion of full-text articles were documented in a characteristic of excluded studies table (Table S1). Among included records, multiple publications on the same study were collated.

2.3.2 | Data extraction and management

Study characteristics and data on predefined outcomes (see 'Eligibility criteria') from included studies were extracted by one reviewer (CA-H), the accuracy and correctness of the extractions were verified by a second reviewer (HE), and disagreements were resolved by consensus. Because of a high heterogeneity in outcome reporting, we used the term 'asymptomatic/improved' whenever the interventional drug prevented or improved neurological or liver-related symptoms. For assessment of 'asymptomatic/improved' events, there was no distinction between symptom relief and symptom improvement. Where available, outcome data were extracted in conjunction with the clinical presentation of the patients at diagnosis as reported by the authors, that is, presymptomatic patients (without clinical manifestations), and patients with hepatic, hepato-neurological or neurological manifestations. When study cohorts included drug switcher patients, we considered patient data only for the first-line treatments until the time of drug switch. If the outcome was not reported at the time of drug switch, we censored the patient from that outcome analysis. However, for the extraction of mortality and OLT, we included all patients and grouped them according to their first-line treatments (according to the intention-to-treat principle). From two studies,[32,33] outcome data of first-line treatments were re-extracted from clinical files by one reviewer (KHW).

2.3.3 | Assessment of risk of bias in included studies

The quality of included observational studies and non-randomized trials was assessed on study level using the Newcastle-Ottawa scale (NOS) for cohort studies by one reviewer (CA-H). The scale applies a semi-quantitative star system (0-9 stars, with more stars indicating higher quality) to estimate study quality in the three domains subject selection, comparability of cohorts, and assessment of outcome.[34] Quality appraisal of randomized controlled trials was conducted using the RoB 2.0 tool which was developed by the Cochrane collaboration.[35]

2.3.4 | Statistical analysis

We performed a meta-analysis for pooling odds ratios (ORs) for studies that were considered sufficiently clinical homogenous. The primary outcomes were mortality and asymptomatic/improved, the secondary outcomes side effects, early neurological deterioration, treatment discontinuation and OLT. In the case that at least six studies without zero events could be included in the meta-analysis,[36,37] we performed inverse-variance random effects meta-analyses using the Paule-Mandel between study heterogeneity estimator with modified Hartung-Knapp confidence intervals (CIs).[38,39] For consistency, we used the same model for sensitivity analyses irrespective of the number of studies. For any comparison with zero events or less than six included studies, we used beta-binomial models which show satisfactory statistical properties for pooling sparse data.[40] In addition to the beta-binomial models, we performed sensitivity analyses using the Peto-Method because effect estimates and confidence intervals can strongly depend on the applied meta-analytic method in sparse data and unbalanced study arm situations.[41] For all pooled ORs, we calculated 95% CIs. Statistical heterogeneity was quantified with I^2.[42] If the I^2 value was >0%, we calculated 95% prediction intervals in addition to the 95% CIs.[43] We performed sensitivity analyses according to methodological study quality if at least five moderate to high-quality studies (NOS score <6 as was rated as low quality and ≥6 as moderate to high quality[44]) were available. Subgroup analyses according to clinical presentation were added when at least three studies reported subgroup-specific outcome data. We could not prepare funnel-plots because all comparisons included less than ten studies.

For inverse-variance random effects and Peto-odds-ratios meta-analyses, we used the R package meta.[45] We performed meta-analyses based beta-binomial models with SAS© Version 9.4. For the graphical representation of beta-binomial analyses, we generated forest plots in R using the fixed-effect inverse variance model and manually inserted the summary OR derived from the beta-binomial model.

3 | RESULTS

3.1 | Results of the search and study characteristics

Our electronic searches identified 3,450 records and three potentially eligible additional records were found using backward citation chasing. Eight potentially relevant records were excluded because of foreign language.[46-53] A total of 174 records were selected for full-text screening to assess eligibility. Of these, 26 publications reporting on 23 studies met our inclusion criteria (Figure 1).[17,26,32,33,54-7375,76] Reasons for exclusion of the 148 studies are shown in Table S1.

The included studies were published between 1968 and 2018. Of the 23 studies, 17 were retrospective observational studies, three were prospective observational studies, two were non-randomized controlled trials and one was a randomized controlled trial (Table 1). Given the substantial ambiguity in the classification of observational studies,[74] we refrained from defining observational study designs any further.

From the included studies (Table 1), four compared the use of DPen with no treatment[54-56,59] (of which one study[55] used a mixture of DPen and L-penicillamine, the less-active stereoisomer of DPen). Four compared DPen with trientine or Zn,[33,70,73,75] 11 compared DPen with Zn[17,26,57,60,62,64,67-69,71,76] and two DPen with trientine.[32,61] Finally, two stand-alone studies evaluated the performance of DPen vs succimer treatment during maintenance phase[58] and trientine vs TTM treatment as initial therapy,[63] respectively. In both studies, all patients received Zn treatment concomitantly to the drugs under evaluation. Only two[57,64] of the 26 included publications were already analysed in the previous systematic review on optimal initial treatment of Wilson's disease.[22]

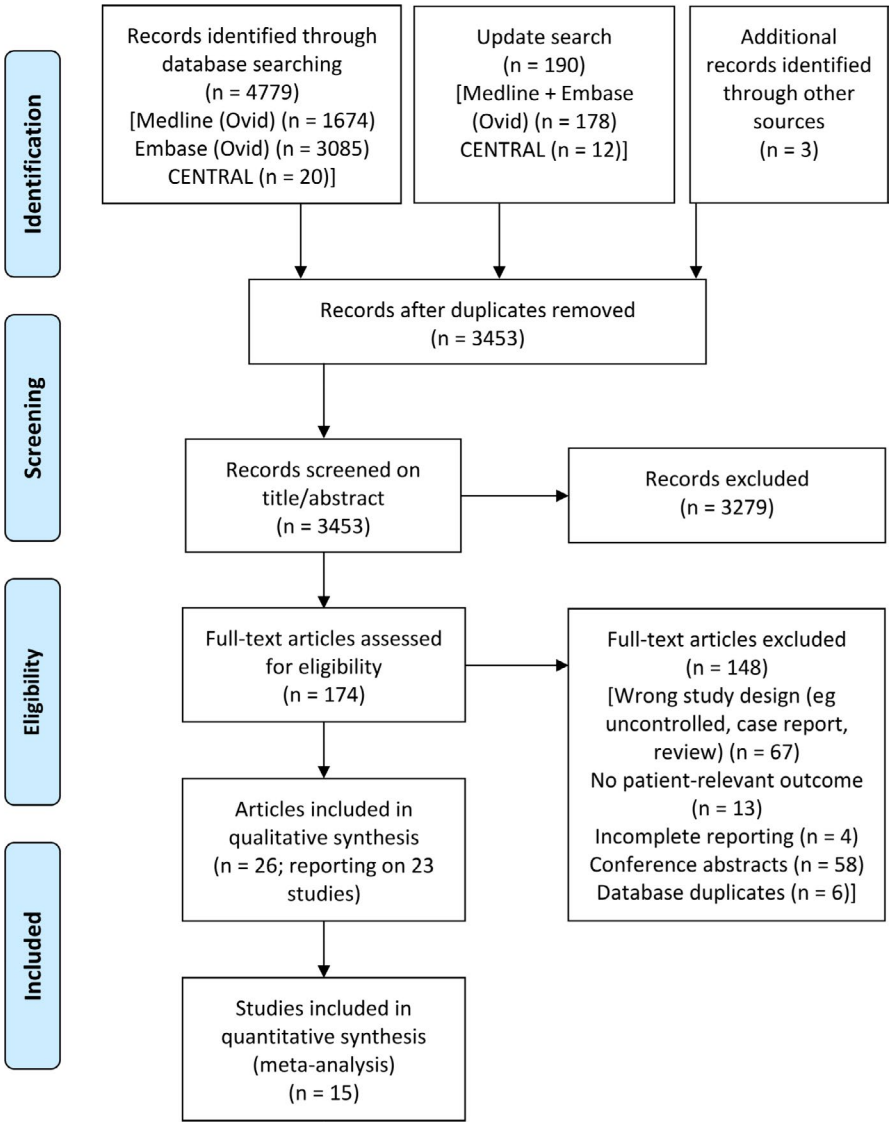

FIGURE 1 Study flow diagram for the selection of studies

TABLE 1 Characteristics of included studies: Overview

First author country year	Study design	Patient population, study duration	Treatment comparison	Outcome(s)	Presentation	Patients (n) [original sample size]
Goldstein United States 1968[54]	Retrospective observational study	• Cases prior 1958: no Dpen available • 3 sibling pairs • Mean age 26 (5-48) y • Mean TD 58 (1-114) mo	Dpen vs no treatment	Mortality asymptomatic/ improved	All Presymptomatic (Dpen) Hepatic (Dpen) Hepato-neurological (Dpen) Neurological (Dpen) Hepatic (-) Hepato-neurological (-)	23[26] 2[2] 1[1] 4[5] 1 too early for evaluation 14[15] 1 too early for evaluation 1[2] 1 lost to FU 1[1] Excluded from original sample size: 1 patient dimercaprol
Sternlieb United States 1968[55]	Retrospective observational study	• Presymptomatic patients with family history and/or established WD diagnosis • No Dpen, if Dpen not available or diagnosis only presumptive • Mean age 9 (1-34) y • Mean FU 44 (6-108) mo	Dpen or D/Lpen vs no treatment	Mortality asymptomatic	All Presymtomatic (Dpen or D/ Lpen) Presymtomatic (-)	53[53] 42[42] 11[11]
Strickland Taiwan/United Kingdom 1973[56]	Retrospective observational study	• WD diagnosis partially done post-mortem • Including sibling pairs • Frequently, Dpen not available (despite WD diagnosis) • Mean age 15 (5-47) y • Mean TD 126 (1-180) mo	Dpen vs no treatment	Mortality asymptomatic	All Presymtomatic (Dpen) Symptomatic (Dpen) Presymtomatic (-) Symptomatic (-)	88[88] 16[16] 35[35] 1[1] 36[36] Excluded from original sample size: 54 patients FU uncompleted
Durand France/Israel/ Switzerland 2001[59]	Retrospective observational study	• All patients had liver injury, non-WD causes of liver injury excluded • Manifestations less than 2 mo before admission • Cases prior 1979: No Dpen because considered ineffective • Mean age 17 (8-22) y • Mean FU 72 (3-144) mo	Dpen vs no treatment	Mortality OLT	All Hepatic (Dpen) Hepatic (-)	17[17] 11[11] 6[6]

(Continues)

TABLE 1 (Continued)

First author country year	Study design	Patient population, study duration	Treatment comparison	Outcome(s)	Presentation	Patients (n) [original sample size]
Weiss Germany/ Austria 2011[33,a] (Merle, 2007[65])[a]	Retrospective observational study	• WD diagnosis 1954-2008 • Patients referring to hepatology centres • Treatment for ≥6 mo • Median age 18 (1-57) y • Median FU 205 (5-649) mo	Dpen vs Trientine vs Zn-(sulphate/ acetate)	Mortality asymptomatic/ improved side effects treatment discontinuation neurological deterioration	All Presymptomatic (Dpen) Hepatic (Dpen) Hepato-neurological (Dpen) Neurological (Dpen) Presymptomatic (Trientine) Hepatic (Trientine) hepato-neurological (Trientine) Neurological (Trientine) Hepatic (Zn) Neurological (Zn)	267[267] 29[29] 131[131] 19[19] 41[41] 1[1] 13[13] 5[5] 5[5] 18[18] 5[5] Excluded from original sample size: 21 patients Zn+chelator
Sini Italy 2013[70]	Retrospective observational study	• WD diagnosis • Patients referring to hepatology centre • Consent to serial liver biopsies • Mean age 23 (5-51) y • Median FU 300 (NR) mo	Dpen vs Trientine vs Zn (sulphate/ acetate)	Fibrosis progression	All Hepatic (Dpen) Hepato-neurological (Dpen) Hepatic (Trientine) Hepatic (Zn) Hepato-neurological (Zn)	17[23] 12[16] 4 switchers 2[3] 1 switch trientine 0[1] 1 switch Zn 1[1] 2[2] Excluded from original sample size: 17 patients combination therapy
Seessle Germany 2016[73,a]	Retrospective observational study	• WD diagnosis 1998-2009 • Patients referring to hepatology centre • Treatment for ≥6 mo	Dpen vs Trientine vs Zn-(sulphate/ acetate)	Autoimmune diseases	All Any (Dpen) Any (Trientine) Any (Zn)	207[207] 91[91] 58[58] 58[58]
Tai Taiwan 2018[75]	Retrospective observational study	• Random sample from national database 2000-2011 • WD subjects identified according to ICD-9 code 275.1 • Median age 25 (3-63) y • Median FU 78 (5-146) mo	Dpen vs Trientine vs Zn	Treatment discontinuation	All Any (Dpen) Any (Trientine) Any (Zn)	37[66] 25[54] 5 switch trientine, 24 switch Zn 4[4] 8[8]
Czlonkowska Poland 1996[57]	Non-randomized controlled trial	• WD diagnosis since 1980 • Fully compliant • Patients referring to neurological centre • Mean age 29 (NR) y • Mean FU 58 (NR) mo	Dpen vs Zn-sulphate	Asymptomatic/ improved mortality side effects treatment discontinuation	All Presymptomatic (Dpen) Hepatic (Dpen) Neurological (Dpen) Presymptomatic (Zn) Hepatic (Zn) Neurological (Zn)	48[67] 2[3] 1 switch Zn 3[4] 1 switch Zn 14[27] 13 switch Zn 8[8] 3[3] 18[22] 4 switch Dpen

(Continues)

TABLE 1 (Continued)

First author country year	Study design	Patient population, study duration	Treatment comparison	Outcome(s)	Presentation	Patients (n) [original sample size]
Iorio Italy 2004[60,b]	Retrospective observational study	• WD diagnosis 1979-2001 • Patients referring to paediatric departments • Treatment for ≥12 mo • Median age 7 (1-18) y • Median TD 76 (12-271) mo	Dpen vs Zn-sulphate	Asymptomatic/ improved side effects OLT treatment discontinuation	All Presymptomatic (Dpen) Hepatic (Dpen) Neurological (Dpen) Presymptomatic (Zn) Hepatic (Zn) Neurological (Zn)	109[109] 3[3] 80[80] 4[4] 4[4] 16[16] 2[2]
Czlonkowska Poland 2005[62]	Prospective observational study	• WD diagnosis 1992-2003 • Patients referring to neurological centre • Mean age 25 (NR) y	Dpen vs Zn-sulphate	Mortality	All Any (Dpen) Any (Zn) Any (-)	160[164] 79[79] 81[81] 0[4] 4 diagnosis too late
Medici Italy 2006[64]	retrospective observational study	• WD diagnosis since 1980 • Mean age 16 (4-35) y • Mean FU 180 (NR) mo	Dpen vs Zn-sulphate (acetate)	Asymptomatic/ improved side effects treatment discontinuation early neurological deterioration OLT mortality	All Hepatic (Dpen) Hepato-neurological (Dpen) Hepatic (Zn) Hepato-neurological (Zn)	35[35] 15[15] 8[8] 8[8] 4[4]
Svetel Serbia 2009[67]	Prospective observational study	• WD diagnosis 1980-2007 • Symptomatic patients • Mean age 24 (NR) y • Mean FU 133 (NR) mo	Dpen vs Zn-sulphate	15 y probability of survival	All Symptomatic (Dpen) Symptomatic (Zn)	89[89] 79[79] 10[10] Excluded from original sample size: 32 patients Zn+Dpen
Cope-Yokoyama Italy 2010[26]	Prospective observational study	• WD diagnosis 1981-2006 • Patients referring to hepatology centre • Consent to serial liver biopsies • No alcohol abuse, hepatitis virus, or metabolic syndrome • Mean age 17 (6-35) y • Mean FU (12-144) mo	Dpen vs Zn-sulphate	Fibrosis progression	All Hepatic (Dpen) Hepatic (Zn)	11[12] 5[5] 6[7] 1 switch Dpen
Bruha Czech Republic 2011[68]	Retrospective observational study	• WD diagnosis 1965-2008 • Mean age 39 (16-63) y • Mean FU 181 (12 492) mo	Dpen vs Zn-(sulphate/ acetate)	asymptomatic/ improved side effects treatment discontinuation	All Presymptomatic (Dpen) Hepatic (Dpen) Neurological (Dpen) Presymptomatic (Zn) Hepatic (Zn) Neurological (Zn)	93[112] 8[9] 1 switch Zn 34[40] 6 switch Zn 38[50] 12 switch Zn 2[2] 8[8] 3[3] Excluded from original sample size: 3 patients with OLT and no treatment 2 patients Zn+Dpen

(Continues)

TABLE 1 (Continued)

First author country year	Study design	Patient population, study duration	Treatment comparison	Outcome(s)	Presentation	Patients (n) [original sample size]
Rodriguez Spain 2012[69]	Retrospective observational study	• WD diagnosis 1975-2010 • Including siblings • Comorbidities in >50% of patients • Symptomatic patients treated with Dpen • Median age 22 (6-50) y • Median FU 168 (24-408) mo	Dpen vs Zn	Asymptomatic/ improved side effects treatment discontinuation OLT	Hepatic (Dpen) Hepato-neurological (Dpen) Neurological (Dpen) Presymptomatic (Zn)	10[10] 3[3] 5[5] 2[2]
Ranucci Italy 2014[71,b]	Retrospective observational study	• WD diagnosis in childhood (1984-2012) • Patients referring to hepatology centre with mild liver disease • Symptomatic patients preferentially treated with Dpen • Treatment for ≥6 mo • Median age 6 (1-16) y • Median FU 144 (19-302) mo	Dpen vs Zn-(sulphate/ acetate)	Asymptomatic/ improved side effects neurological deterioration treatment discontinuation mortality OLT	All Hepatic (Dpen) Hepatic (Zn)	42[42] 27[27] 15[15]
Czlonkowska Poland 2014[17] (Litwin, 2015[72])	Retrospective observational study	• WD diagnosis in adulthood (2005-2009) • Patients referring to neurological centre • Symptomatic patients • Median age 22-33 (NR) y • Median FU 48 (NR) mo	Dpen vs Zn-sulphate	Asymptomatic/ improved side effects treatment discontinuation mortality early neurological deterioration	All Hepatic (Dpen) Neurological (Dpen) Hepatic (Zn) Neurological (Zn)	143[143] 36[36] 35[35] 51[51] 21[21]
Vieira Barbosa Switzerland 2018[76]	Retrospective observational study	• WD diagnosis in adulthood (2004-2016) • Patients referring to hepatology centre • Symptomatic patients • Median age 26 (18-56) y	Dpen vs Zn-acetate	Treatment discontinuation mortality OLT	All Hepatic (Dpen) Hepatic (Zn)	3[8] 3[6] 3 switch trientine 0[2] 2 switch Dpen Excluded from original sample size: 2 patients with OLT and no treatment
Kumagi Japan 2004[61]	Retrospective observational study	• WD diagnosis 1976-2003 • All patients showed hepatic manifestations • No hepatitis virus in most patients • 4 cases with family history and 4 siblings • Mean age 32 (9-66) y • Median FU 48 (1-180) mo	Dpen vs Trientine	Mortality OLT side effects treatment discontinuation	All Presymptomatic (Dpen) Hepatic (Dpen) Hepato-neurological (Dpen) Hepatic (T)	13[16] 1[1] 10[10] 4[4] 1[1]

(Continues)

TABLE 1 (Continued)

First author country year	Study design	Patient population, study duration	Treatment comparison	Outcome(s)	Presentation	Patients (n) [original sample size]
Weiss Germany/ Austria/ Eurowilson 2013[32,a]	Retrospective observational study	• WD diagnosis 1956-2010 • Patients referring to tertiary care centres or under trientine monotherapy from EUROWILSON registry • Treatment for ≥6 mo • Median age 18 (1-60) y • Median FU 160 (NR) mo	Dpen vs Trientine	Asymptomatic/ improved side effects treatment discontinuation early neurological deterioration	All Presymptomatic (Dpen) Hepatic (Dpen) Hepato-neurological (Dpen) Neurological (Dpen) Presymptomatic (trientine) Hepatic (trientine) Hepato-neurological (trientine) Neurological (trientine)	333[333] 48[48] 150[150] 31[31] 66[66] 2[2] 20[20] 7[7] 9[9] Excluded from original sample size: 72 first-line treatments other than Dpen or trientine
Ren China 1998[58]	Non-randomized controlled trial	• WD diagnosis 1994-1997 • Trial on maintenance treatment (patients initially treated with unithiol or EDTA) • Mean age 19 (NR) y • Mean FU 18 (6-36) mo	Dpen+Zn-gluconate vs Succimer+Zn-gluconate	Asymptomatic/ improved side effects treatment discontinuation	All Presymptomatic (Dpen) Hepatic (Dpen) Neurological (Dpen) Presymptomatic (Succimer) Hepatic (Succimer) Neurological (Succimer)	120[120] 10[10] 9[9] 41[41] 10[10] 10[10] 40[40]
Brewer United States/ Canada 2006[63] (Brewer, 2008[66])	Randomized controlled trial	• Start of enrolment 1994 • Symptomatic patients • Treatment-naive or chelator treatment for <28 d or long-term treatment stopped for >1 y with development of new symptoms • Trial on initial treatment (patients subsequently treated with Zn-acetate for maintenance) • Mean age 28 (13-49) y • TD 2 mo	Trientine+Zn-acetate vs TTM+Zn-acetate	Early neurological deterioration mortality side effects	All Neurological (Trientine) Neurological (TTM)	48[48] 23[23] 25[25]

Abbreviations: Age, age at admission; d, days; DPen, D-penicillamine; EDTA, ethylenediaminetetraacetic acid; FU, follow-up; mo, months; NR, not reported; OLT, orthotopic liver transplantation; TD, treatment duration; TTM, tetrathiomolybdate; WD, Wilson's disease; y, years; Zn, zinc salts.

[a]Likely cohort overlap (Heidelberg University Hospital).

[b]Likely cohort overlap (University of Naples).

The studies included 2055 patients, whereas a partial overlap of cohorts was identified between three studies from Heidelberg, Germany,[32,33,73] and two studies from Naples, Italy.[60,71] Some studies exclusively included presymptomatic,[55] hepatic,[26,59,71,76] neurological[63] or symptomatic[17,64,67,70] (ie with any manifestations) patients (Table 1). The age range across all studies was 1-66 years; 17 of the 23 studies included mixed populations while five studies reported on children[60,71] or adults[17,68,76] only.

Mortality,[17,54-57,59,61-64,71,76] "asymptomatic/improved",[17,32,33,54,57,58,60,64,68,69,71] side effects[32,33,57,58,60,61,63,64,68,69,71] and treatment discontinuation[17,32,33,57,58,60,61,64,68,69,71,75,76] were the most prevalent outcomes, followed by OLT[59-61,64,69,71,76] and neurological deterioration[17,32,33,63,64,71] (Table 1). Data on fibrosis progression,[26,70] development of autoimmune diseases[73] and 15-year probability of survival[67] were reported in stand-alone studies only. The maintenance phase of drug therapy was specifically addressed in only one study.[58]

3.2 | Methodological study quality rating

The NOS scores ranged between 2 and 8 with a median score of 5.5 (Table S2), indicating that only a subset of studies were of high or moderate quality. Potential problems with the representativeness of included patients and comparability of patients between different treatment arms (selection bias) were identified in 9 of the 21 studies (38%).[26,33,56,59,61,67,69,71,76] Only four studies reached a NOS score >7, which is indicative of high reliability.[17,54,57,70] Adjusting for confounding factors was reported in only one study.[17] Quality assessment of Brewer et al[63] using RoB 2.0 identified some concerns with regard to bias because of the randomization process, missing outcome data, and in the selection of the reported results (Table S2).

3.3 | Data synthesis and analysis

3.3.1 | D-Penicillamine vs no treatment

In the four studies comparing DPen-treated and untreated WD patients,[54-56,59] the pooled OR for death was 0.013 (95% CI 0.0010 to 0.17; I^2 = 31%; Figure 2, Table 2). The pooled OR for remaining or becoming asymptomatic was 22.3 (95% CI 0.40 to 1.2 x 10^3; I^2 = 86%; Table 2).[54-56] Other outcomes were not reported for this comparison. Because of the low number of studies no sensitivity or subgroup analyses were performed.

3.3.2 | D-Penicillamine vs zinc salts

The pooled OR for mortality from seven studies[17,33,57,62,64,71,76] was 0.73 (95% CI 0.16 to 3.40; I^2 = 37%; Figure 3A, Table 2). For the asymptomatic/improved outcome, meta-analysis of seven studies[17,33,57,60,64,68,69] yielded an OR of 0.84 (95% CI 0.48 to 1.48; I^2 = 0%; Figure 3B, Table 2).

The pooled OR for OLT[60,64,69,76] was 1.74 (95% CI 0.066 to 46.0; I^2 = 37%; Table 2). Side effects[33,57,60,64,68] and neurological deterioration[17,33,64,71] yielded ORs of 3.28 (95% CI 0.542 to 19.9; I^2 = 24%; Figure S1, Table 2) and 3.71 (95% CI 0.42 to 32.7; I^2 = 10%; Figure S2, Table 2), respectively. The pooled OR of treatment discontinuation[17,33,57,60,64,68,69,75,76] was 2.96 (95% CI 1.14 to 7.66; I^2 = 48%; Figure S3, Table 2).

One study found more patients treated with DPen (6/91, 6%) to develop autoimmune diseases as compared to Zn (0/58) or trientine (0/58).[73] One study detected no difference between DPen- and Zn-treated patients for the 15-years probability of survival (78 ± 6% vs 67 ± 17%).[67] Focusing on progression of liver fibrosis, one study found a higher rate of progression in the DPen group (1/14, 7%) compared to Zn (0/3).[70] Another study found a higher rate of progression in the Zn group (2/5, 40%) compared to DPen (0/3).[26] Extracted outcome data from individual studies are reported in Table S3.

Sensitivity analyses using the Peto-Method or excluding low-quality studies did not fundamentally change the results (Table 2). However, the results from the Peto-Method suggested that DPen may have a higher frequency of side effects, neurological deterioration and treatment discontinuation than Zn (Table 2). Subgroup analyses according to the clinical presentations 'hepatic' and '(hepato-) neurological' also did not fundamentally change the results (Table 2). Other sensitivity or subgroup analyses including presymptomatic patients were not possible because of the low number of studies.

3.3.3 | Other comparisons

There were not enough studies comparing other drug combinations to perform meta-analysis. For the comparisons trientine with

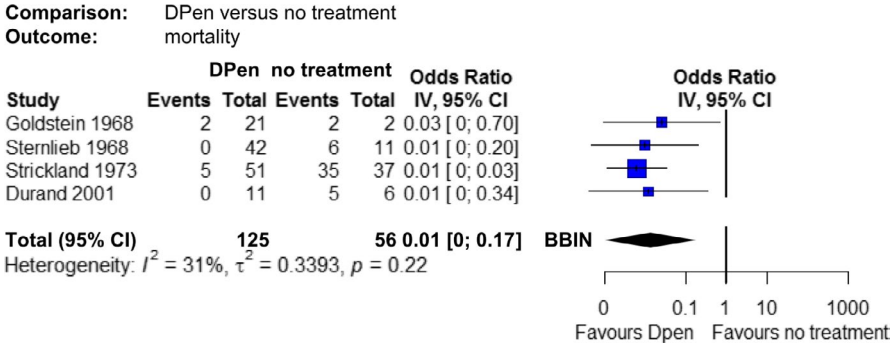

FIGURE 2 Meta-analysis of DPen vs no treatment. Effect of DPen vs no treatment on all-cause mortality. Summary odds ratio derived from beta-binomial model (BBIN); box sizes reflect the weights of the fixed-effect inverse variance model (IV)

TABLE 2 Summary of results

Outcome	# Studies	# Patients	Method	Effect estimate (OR)	95% CI	I^2 (%)	Prediction interval
D-Penicillamine vs no treatment							
Mortality	4	125 vs 52	BBIN	0.013	0.0010-0.17	31	0-0.53
			Peto	0.02	0.01-0.05		
Asymptomatic	3	114 vs 50	BBIN	22.3	0.40-1.2 x 10^3	86	0-2.1 × 10^{15}
			Peto	NA	NA		
D-Penicillamine vs zinc salts							
Mortality	7	460 vs 238	BBIN	0.73	0.16-3.40	37	0.01-71.46
			Peto	1.14	0.55-2.33		
Asymptomatic/improved	7	518 vs 173	PM-HK	0.84	0.48-1.48	0	NA
Asymptomatic/improved (sensitivity[a])	5	280 vs 148	PM-HK	0.96	0.43-2.14	12	0.31-2.98
Asymptomatic/improved (subgroup: hepatic)	5	243 vs 100	BBIN	0.59	0.16-2.14	0	NA
			Peto	0.65	0.34-1.25		
Asymptomatic/improved [subgroup: (hepato-) neurological]	4	141 vs 43	BBIN	0.79	0.15-4.14	0	NA
			Peto	0.99	0.40-2.46		
OLT	4	134 vs 38	BBIN	1.74	0.066-46.0	37	0-502.6
			Peto	0.68	0.13-3.40		
Side effects	5	463 vs 103	BBIN	3.28	0.54-19.9	24	0.64-19.28
			Peto	3.68	2.10-6.43		
Neurological deterioration	4	130 vs 45	BBIN	3.71	0.42-32.7	10	0.22-40.02
			Peto	2.86	1.18-6.93		
Treatment discontinuation	9	612 vs 187	PM-HK	2.96	1.14-7.66	48	0.31-27.89
Treatment discontinuation (sensitivity[a])	6	368 vs 160	PM-HK	3.62	1.05-12.51	57	0.41-26.13
Treatment discontinuation (subgroup: hepatic)	6	255 vs 102	BBIN	2.55	0.66-9.93	44	0.26-29.04
			Peto	2.82	1.60-4.98		
Treatment discontinuation [subgroup: (hepato-) neurological]	4	153 vs 33	BBIN	4.49	0.42-48.0	70	0-8.7 × 10^3
			Peto	NA	NA		

Abbreviations: BBIN, Beta-binomial model; CI, confidence interval; NA, not applicable; NOS, Newcastle-Ottawa scale; OR, odds ratio; Peto, Yusuf-Peto method; PM-HK, Paule-Mandel estimator with modified Hartung-Knapp confidence intervals.
Note: We used PM-HK whenever there were at least 6 studies to pool or for sensitivity analyses of PM-HK analyses, we used BBIN whenever there were outcomes with 0 events or less than 6 studies. We did not use Peto when I^2 was >50%. We did not calculate prediction intervals when I^2 was 0%.
[a]Sensitivity analysis for studies rated NOS ≥6; primary outcomes shown in bold, secondary outcomes in non-bold characters.

DPen and trientine with TTM, the authors found no difference in effectiveness in primary outcomes.[32,63] However, they found early neurological deterioration to occur more frequently under therapy with trientine (5/16, 31% or 6/23, 26%) as compared to DPen (8/97, 8%)[32] or TTM (1/25, 4%).[63] At the same time, the relative risk for side effects was found to be lower under trientine therapy (9/38, 24% or 1/23, 4%) compared to DPen (182/295, 62%)[32] or TTM (7/25, 28%).[63] For the comparison between DPen and succimer in the maintenance phase, higher effectiveness (49/60, 82% vs 35/60, 58%) and fewer side effects (9/60, 15% vs 22/60, 37%) and treatment discontinuations (11/60, 18% vs 25/60, 42%) were reported for succimer (Table S3).[58]

4 | DISCUSSION

4.1 | Summary of evidence

In the present review, we aimed to assess the comparative effectiveness of common WD therapies on patient-relevant outcomes. For the comparison of DPen vs no treatment, we found a strong association between DPen and reduced mortality. Given the commonplace that WD was a fatal disease up until the institution of DPen therapy, this result is merely confirmatory. Although DPen therapy as opposed to no treatment is known to be associated with prevention or remission of clinical symptoms, the corresponding meta-analysis

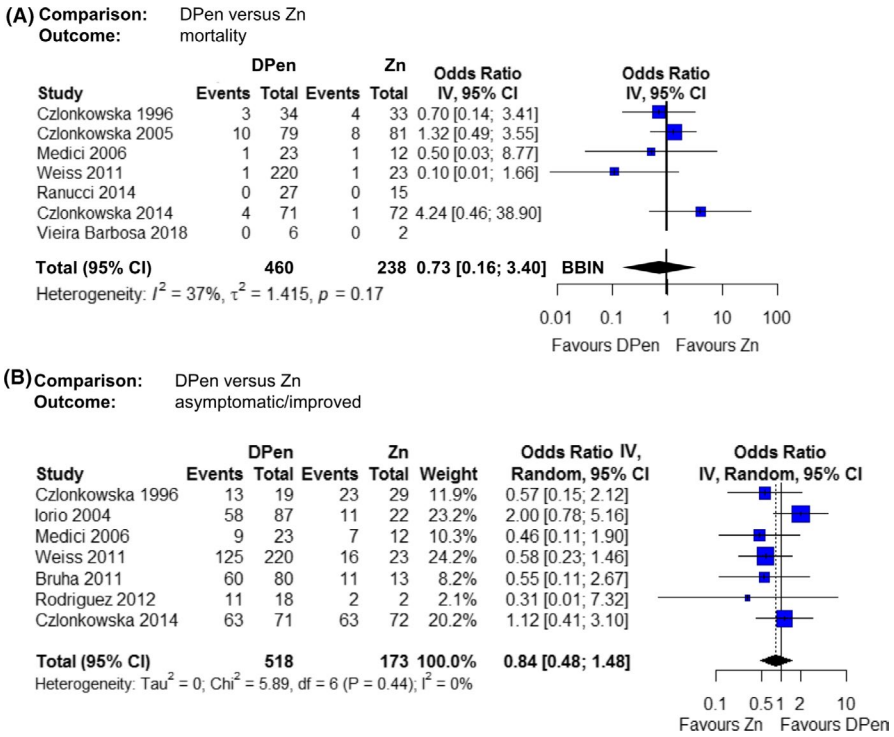

FIGURE 3 Meta-analyses of DPen vs Zn treatment. A, Effect of DPen vs Zn treatment on all-cause mortality. Summary odds ratio derived from beta-binomial model (BBIN); box sizes reflect the weights of the fixed-effect inverse variance model (IV). B, Effect of DPen vs Zn treatment on prevention, remission, or amelioration of clinical symptoms (asymptomatic/improved). Performed with inverse-variance (IV) random effects meta-analysis using the Paule-Mandel between study heterogeneity estimator with modified Hartung-Knapp confidence intervals

with a prediction interval of 0 to 2.1 × 10^{15} could not confirm the clinical experience. This was, however, strongly affected by study heterogeneity and selection bias, as one study included only pre-symptomatic subjects.[55]

For the comparison of DPen vs Zn, we found no evidence for a difference in mortality, clinical symptoms, OLT, side effects and neurological deterioration. For side effects, this lack of evidence could be explained by one outlier study[64] (Figure S1). In this study, 4 patients in the Zn arm with gastrointestinal irritations were counted as events, although two of those four were subsequently switched from Zn-sulphate to Zn-acetate with favourable outcome (see Limitations section for further discussion). Results from sensitivity and subgroup analyses were mostly confirmative, although depending on the analysis used, DPen appeared to have a higher impact on side effects and neurological deterioration than Zn – which lines up with previous conclusions.[22] However, DPen may be associated with more treatment discontinuations than Zn, although data were heterogeneous. We found no indication for subgroup effects in the hepatic and (hepato-) neurological subgroups. Further inspection of the data suggested that, contrary to Zn, the principal reason for DPen treatment discontinuations may have been the appearance of side effects (Table S3 and data not shown). We emphasize that because of moderate/low study quality and heterogeneity, the results from our meta-analyses should in general be interpreted cautiously and graded as low evidence.

One reason why we may not have detected a difference in effectiveness between DPen and Zn may be because of our decision to restrict analyses to the first treatment block, considering that subsequent treatment blocks are confounded by treatment history. This may also be the reason why our findings deviate from previous conclusions that Zn is not as effective as chelator therapy.[33] Another reason may be our choice of analysis: The more conservative beta-binomial meta-analysis but not the Peto-Method resulted in wide confidence intervals crossing the null in most secondary outcomes. Such inconsistency in results across different models reflects once more the considerable clinical and statistical heterogeneity of the included studies.

During our review of all included studies that compared chelator and Zn treatments, we noticed that several authors explicitly indicated Zn as the optimal primary treatment option for certain patient groups including presymptomatic and neurological patients. Interestingly, several authors' recommendations thus stand in contrast to the recommendations in current guideline publications (recommendations and guideline recommendations in Table S4). During title/abstract screening, we also flagged all single-arm studies that investigated Zn monotherapy.[77-84] Most of these studies reported positive effects of Zn. The present review also indicates Zn to display a favourable safety profile and prevent or relieve symptoms in a similar manner as chelator-therapy would, although results were not definitive. However, Zn induces copper excretion indirectly via blocking of intestinal copper

absorption, which is a slow-acting mechanism that takes a few weeks or months to be effective.[10] Hence, using only Zn is not a suitable therapy for patients experiencing acute copper toxicity. A decoppering phase with a chelator applied together with Zn and followed by Zn monotherapy, as introduced by Brewer,[63] may therefore constitute a suitable treatment regimen and form a precedent for future guideline formulation. Alternatively, the non-permanent introduction of a chelator to a patient under long-term Zn treatment[33] may prove useful in case of unmitigated copper toxicity.

Recently, a new formulation of TTM called WTX101 was developed and successfully run through a phase 2 trial.[14] The subsequent phase 3 trial comparing WTX101 with standard of care (chelation or Zn therapy or a combination of both chelation and Zn therapy) is currently running.[15] A major advantage of WTX101 is the once-daily dosing scheme[14] (compared to the more complex 2-times a day dosing scheme under DPen[19]) which could positively impact on patients' compliance and life-long copper control. In the same vein, efforts have been made to validate a once-daily dosing scheme of trientine for maintenance treatment,[85] which currently requires a 2-times dosing scheme.[19] Similar dosing simplification has unfortunately not yet been achieved for Zn which requires at least two doses per day to be effective.[78] However, some prework towards an extended-release formulation of Zn has been published.[86]

Conspicuously, only one of the studies included in this review addressed the maintenance phase of WD therapy comparing DPen+Zn to succimer+Zn.[58] None of the included studies reported on Zn compared to control treatment in the maintenance phase, although Zn is recommended for maintenance treatment almost throughout all international guidelines (Table S4). During title/abstract screening, we identified some single-arm observational studies that documented the potential suitability of Zn for maintenance therapy.[87-92] One reason for the paucity of controlled data on maintenance treatment may be that the field appears to be lacking consensus on the definition of maintenance therapy, that is, when a patient is 'adequately decoppered'.[20]

A further interesting observation we made in included studies was concerned with patients with hepatic symptoms. Several study authors reported an apparent lack of correlation between elevated serum transaminase levels and actual severity of liver disease (Table S5)[26,33,60,64,70] (a correlation that is usually found in the context of liver disease[93] but may be corrupted in WD because of predominance of apoptotic over necrotic hepatocyte death[94,95]). Yet, within these very studies, the rating of treatment success was often, sometimes even exclusively, based on serum transaminase levels. In light of possible lack of correlation between serum transaminase levels and actual severity of liver disease such rating may in fact be misleading. Alternative liver function tests such as other laboratory values (bilirubin, prothrombin time, ammonia, non-ceruloplasmin bound copper) as well as liver stiffness measurements and histological findings should complement the time course analyses of serum transaminases in WD patients. Currently, there is no consensus on a composite of clinical and biochemical markers of liver function to be used to guide treatment decisions.

4.2 | Future research

Future research should consider applying modern methodology such as the combination of randomization and use of routinely collected data. Randomization of the treatment would increase comparability of the groups, reduce selection bias and facilitate causal conclusions from the study results. As such, the results of the ongoing phase 3 trial comparing WTX101 to other common treatments are highly awaited.[15] Given the results of this review and the paucity of controlled clinical data concerning the maintenance phase of WD treatment, it would be highly desirable to compare the WTX101 group of maintenance phase patients to a clean Zn group of randomly allocated patients (not to a heterogeneous 'standard of care' group). So far, a direct comparison of these two drugs is missing from the literature and clinical decisions concerning the maintenance phase of therapy are hardly supported by evidence.

Further research is also needed to unravel the multifaceted factors that influence serum transaminase levels in WD patients and to delineate a reliable biomarker repertoire for the monitoring of liver function in WD. Likewise, we are still lacking a definitive answer as to which treatment is associated with the lowest risk for early neurological deterioration (see below), warranting further studies with more precise reporting. And finally, also less common WD drugs such as Chinese herbals[28] and succimer[58] could be included in future comparative investigations.

4.3 | Limitations

Firstly, the conclusions of our meta-analyses mainly suffer from the fact that high-quality evidence for the comparative effectiveness and safety of WD therapies is scarce. Although DPen and Zn treatment of WD patients has been compared in a fair number of studies, there is not a single randomized controlled trial comparing the two treatments. Moreover, study arms were frequently unbalanced with a bias towards more patients being treated with DPen (Table 1).

Secondly, all studies but one did not statistically correct for any confounding factors. Some factors seem likely to be confounding factors such as age, clinical presentation, disease stage during diagnosis or the specialization of the referral centre performing the study, that is, neurological vs hepatic vs paediatric clinics. The probably most severe limitation, however, comes from selection bias when, for example, study authors would generally prescribe Zn to presymptomatic patients[69] or DPen to patients with hepatic symptoms.[71] We have tried to address some of these limitations by performing sensitivity analyses based on the NOS scores of the studies.

Thirdly, a common yet very limiting problem we encountered were non-uniform definitions of outcomes. We tried to assess early neurological deterioration which is often reported as a side effect in response to treatment initiation in WD patients with neurological presentation.[72,96] Early neurological deterioration is thought to occur more frequently in chelator-treated as compared to Zn-treated patients.[22] In the four studies comparing the effect of DPen vs Zn

on neurological deterioration, differing or intransparent definitions and time windows were used for the scoring of symptoms. Hence, we meta-analysed 'neurological deterioration' in general rather than early neurological deterioration. In the light of these limitations, our meta-analysis on neurological deterioration for the comparison DPen vs Zn should be interpreted with care. It should further be noted that trientine – while apparently the chelator of choice with respect to side effects in general – appears to confer an overproportionally high risk of early neurological deterioration.[32,63] Another example for non-uniform outcome definitions was the scoring of clinical symptoms which was rarely standardized according to published scales.[97-99] We therefore extracted the binary outcome 'asymptomatic/improved' for whenever neurological or liver-related symptoms were reported to be prevented or improved.

Fourthly, we did not assess the severity of different side effects. Thus, relatively mild gastrointestinal irritations which are prevalent among Zn-treated patients (data not shown) were scored equally to severe and irreversible autoimmune disorders or nephrotoxicity which are relatively common among DPen-treated patients (data not shown). Accordingly, our meta-analysis on side effects lends conservative support only to the notion that Zn is safer than DPen.

Fifthly, we did not extract dosing regimens of the WD therapies. Our main reason for neglecting this data was that we did not want to conduct further analyses on the already highly biased, low-quality studies and risk any chance findings. Hence, we cannot exclude an impact of differing dosing regimens on the effect estimates.

Sixthly, we did not differentiate between the use of different zinc salts such as zinc acetate, zinc sulphate and zinc gluconate. This is potentially meaningful, as zinc sulphate may cause more gastrointestinal side effects than zinc acetate.[64,68,100]

5 | CONCLUSIONS

There is not enough evidence to claim superiority of one common WD treatment over the other, a firm basis of controlled clinical data is lacking completely. However, there are some indications that Zn has less side effects and lower treatment discontinuation rate than DPen therapy while being similarly effective. We emphasize that because of low study quality our results should be interpreted cautiously. Future research should focus on higher study quality and reporting.

6 | AUTHOR CONRIBUTIONS

CAH and HE are the guarantors. CAH, HE and RHJH conceived the study. CAH and HE conducted the literature searches. CAH, HE, MLSH and RHJH selected included studies. CAH and KHW extracted the data, HE checked extractions. TM analysed the data. CAH, HE and TM interpreted the results. CAH wrote the first draft and all authors made revisions on the manuscript. All authors read and approved the final version of the article including the authorship list.

ACKNOWLEDGEMENTS

We thank the authors of the primary studies for their timely and helpful responses to our information requests.

CONFLICT OF INTEREST

Four of the included reports are authored by KHW and one by RHJH. KHW is a consultant at Ipsen, Eisai, Chiesi, Vivet therapeutics, GMP-O, Univar, Wilson therapeutics, and BMS, a contract researcher of Univar, Wilson therapeutics, Novartis, QED, Alexion, and GMP-O, and served as a speaker at Novartis, Alexion, Falk and Abbvie. RHJH served on an advisory board for Univar. All other authors declare no financial relationships with any organizations that might have an interest in the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Appenzeller-Herzog C, Mathes T, Heeres MLS, Weiss KH, Houwen RHJ, Ewald H. Comparative effectiveness of common therapies for Wilson disease: A systematic review and meta-analysis of controlled studies. *Liver Int*. 2019;00:1–17. https://doi.org/10.1111/liv.14179