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## Practical insights into chronic management of hepatic Wilson's disease

Erica Nicola Lynch, Claudia Campani, Tommaso Innocenti, Gabriele Dragoni, Paolo Forte, Andrea Galli

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### Abstract

Wilson's disease (WD) is a rare inherited disorder of human copper metabolism, with an estimated prevalence of 1:30000-1:50000 and a broad spectrum of hepatic and neuropsychiatric manifestations. In healthy individuals, the bile is the main route of elimination of copper. In WD patients, copper accumulates in the liver, it is released into the bloodstream, and is excreted in urine. Copper can also be accumulated in the brain, kidneys, heart, and osseous matter and causes damage due to direct toxicity or oxidative stress. Hepatic WD is commonly but not exclusively diagnosed in childhood or young adulthood. Adherent, non-cirrhotic WD patients seem to have a normal life expectancy. Nevertheless, chronic management of patients with Wilson's disease is challenging, as available biochemical tests have many limitations and do not allow a clear identification of non-compliance, overtreatment, or treatment goals. To provide optimal care, clinicians should have a complete understanding of these limitations and counter-balance them with a thorough clinical assessment. The aim of this review is to provide clinicians with practical tools and suggestions which may answer doubts that can arise during chronic management of patients with hepatic WD. In particular, it summarises current knowledge on Wilson's disease clinical and biochemical monitoring and treatment. It also analyses available evidence on pregnancy and the role of low-copper diet in WD. Future research should focus on trying to provide new copper metabolism tests which could help to guide treatment adjustments.



**Key Words:** Wilson's disease; Urinary copper excretion; Non-ceruloplasmin-bound copper; D-penicillamine; Trientine; Zinc salts

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**Core Tip:** Wilson's disease (WD) is rare but curable. Chronic management of WD can be challenging as copper metabolism tests are not standardised. This review provides a broad guidance for the monitoring and treatment of patients with WD. It also analyses available evidence on pregnancy and the role of low-copper diet in WD.

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## INTRODUCTION

Wilson's disease (WD) is a rare autosomal recessive disease which leads to the accumulation of copper. WD is due to defective mutations of the ATP7B gene, which encodes an ATPase that is responsible for the biliary excretion of copper and its incorporation into apo-ceruloplasmin to form holo-ceruloplasmin. Holo-ceruloplasmin is the enzymatically active form which has catalytic and antioxidant activity and delivers copper ions to the organism[1]. In healthy individuals, the bile is the main route of elimination of copper[1]. In WD patients, copper accumulates in the liver and is released into the bloodstream, where it circulates loosely bound to albumin, transcuprein, and low molar mass molecules[2]. Finally, it is excreted in urine. Copper can also be accumulated in the brain, kidneys, heart, and osseous matter and causes damage due to direct toxicity or oxidative stress[3]. WD mainly has hepatic, neurologic, psychiatric, or mixed manifestations.

## PREVALENCE AND CLINICAL MANIFESTATIONS

In 2020, Sandahl *et al*[4] analysed recent literature and results based on different methodologies and produced an updated estimate of the prevalence of WD disease of 1:30000-1:50000, which appeared to be valid for United States, Europe, and Asia; their findings were surprisingly close to the "Scheinberg-Sternlieb Estimate" proposed in 1984. The estimated prevalence is higher in some particular regions due to increased frequencies of the disease-causing mutations and/or more first-cousin parenthoods (*e.g.*, Sardinia, Italy, 1:8700)[4]. In a recent study conducted in Greece, 57.1% of WD patients were asymptomatic at diagnosis (with only mildly elevated liver enzymes), 20.6% of patients suffered from neurological disease, 12.7% had an overt liver disease, 6.3% of patients suffered from acute liver failure, and 3.2% had other manifestations[5]. Specifically, 36.5% of patients were already cirrhotic at time of diagnosis[5]. The most common neurological manifestations are dysarthria (91%), gait disturbance (75%), risus sardonicus (72%), dystonia (69%), rigidity (66%), tremor (60%), and dysphagia (50%)[6]. Approximately 50% of patients with neurologic symptoms have liver cirrhosis at the time of diagnosis. It is unclear whether there are WD patients with neurologic symptoms without any liver involvement. WD can present at any age, although it is most frequently diagnosed in patients between the ages of 5 and 35, with neurologic patients being generally older than those with hepatic manifestations[7].

### Asymptomatic patients with WD

Family screening for WD with ATP7B gene mutational analysis has led to an increase in the identification of asymptomatic siblings with homozygous or compound heterozygous pathological mutations for WD. The most recognised diagnostic score for WD, the Leipzig scoring system, allows the diagnosis of WD on the basis of compatible mutations on both chromosomes, without requiring altered copper metabolism tests[7]. In most cases, asymptomatic siblings with a positive genetic test are considered to have mild liver disease and are started on treatment for WD. The disease is considered fully penetrant, so, according to current guidelines, its genetic diagnosis is a mandatory indication for copper-depleting treatment, although not all gene changes have been established as causing WD[7-9].

Członkowska *et al*[8] reported the case of an 84-year-old woman, who was diagnosed with WD at the age of 54 years and refused anti-copper treatment. The only clinical manifestation of her disease were Keiser-Fleischer rings. Her ceruloplasmin levels were normal and urinary copper excretion (UCE) was



slightly elevated (90 µg/24 h, normal values below 50 µg/24 h). Stättermayer *et al*[10] suggest that asymptomatic siblings diagnosed by genetic screening require further testing before initiating treatment, as they reported two patients carrying two disease-causing mutations who did not have any evidence of altered copper metabolism. In a French study by Collet *et al*[11], 697 indiscriminate subjects were tested for WD mutations: a considerable discrepancy between the heterozygous carrier frequency and the clinical prevalence of WD was found which could be explained by incomplete penetrance or to modifiers genes. On the other hand, it should be noted that there are a few reported cases of pre-symptomatic siblings with only mild biochemical alterations, but with histological evidence of advanced liver disease at diagnosis[12]. Hence, the Leipzig scoring system could be modified in the future as genetic testing might not be considered sufficient to diagnose WD, although further studies are needed to better understand the complex pathophysiology and clinical variability of WD.

## TREATMENT

### **D-Penicillamine**

D-penicillamine (DPA) is the first oral copper chelating agent which was approved for the treatment of WD in 1956[13]. Until then, the only available chelating agent was dimercaprol, a parenterally administered drug still used for the treatment of arsenic, gold, copper, and mercury poisoning, as well as for severe symptomatic WD[14]. DPA binds to extracellular copper and promotes its urinary excretion. Moreover, DPA may also induce the release of intracellular stores of metallothionein, an endogenous copper chelator[15,16]. DPA should be administered at least 1 h before or 2 h after meals, as food inhibits its absorption by almost fifty percent[7]. DPA should be started at a daily dose of 250-500 mg. It should be gradually increased by 250 mg/d every 4-7 d up to 1000-1500 mg/d (2-4 divided doses) to reduce the risk of adverse events (AE) and of paradoxical worsening in patients with predominantly neurologic symptoms[9]. The daily dose can be reduced to 750-1000 mg (2 divided doses) during maintenance[9]. DPA can be also used in children at a dose of 20 mg/kg/d[9]. DPA is associated with numerous AE, which cause treatment discontinuation in approximately 30% of patients[17,18]. Early AE (during the first 3 wk of treatment) include fever, generalized pruritus and rashes, lymphadenopathy, and proteinuria[9]. Moreover, the risk of deterioration of neurologic manifestations increases during the first weeks of treatment in patients with neurologic manifestations of WD and worsening of neurological symptoms has been reported in up to 50% of patients[9,19,20]. Litwin *et al*[21] showed that in 143 symptomatic WD patients a neurological worsening at the beginning of anti-copper therapy occurred in over 10% of patients. The Authors stated that special attention should be paid to those with severe initial neurological manifestations, advanced brain injury, and to those on therapy with dopamine receptor antagonists. In a more recent study by Zhang *et al*[22], 33.8% of patients exhibited significant neurological deterioration after the first 4-weeks of DPA monotherapy. The underlying mechanism causing neurological worsening at treatment initiation seems to be related to a rapid mobilization of unbound copper which triggers a cytotoxic effect in neuronal tissue[23]. Late AE include progressive proteinuria, gastric symptoms, hair loss, hypogeusia, leukopenia, thrombocytopenia, or total aplasia due to bone marrow depression, and myasthenia- or lupus-like syndrome marked by haematuria and positive antinuclear antibody[24]. Finally, elastosis perforans serpiginosa, pemphigus or pemphigoid-like lesions, lichen planus, and aphthous stomatitis have been reported[25].

### **Trientine**

Trientine has been approved as oral copper-chelating agent in 1969. It leads to a hepatic improvement in more than ninety percent of patients with WD mainly affecting the liver[26]. Trientine increases UCE similarly to DPA. In some countries it is only available as a second-line treatment. Trientine gastrointestinal absorption appears to be reduced if compared with DPA, and therefore trientine should be assumed 1 h before or 3 h after meals[7,9]. The initial daily dose of trientine is 20 mg/kg (in 2-4 divided doses), which can be reduced to 15 mg/kg during follow-up. There is no established weight-based dose for the paediatric population and most of the experts use the dose of 20 mg/kg/d with similar dosing frequency as in adults[9]. Trientine is associated with fewer side effects compared with DPA. First of all, the paradoxical neurological worsening at treatment initiation was believed to be less frequent[9,27], although more recent retrospective studies have observed a comparable incidence of paradoxical worsening in patients treated with DPA, trientine, and zinc salts[20,26]. Secondly, bone marrow suppression with thrombocytopenia and leukopenia is rare in patients on trientine, and it should prompt evaluation to identify possible copper deficiency from the overtreatment[23]. Moreover, a reduced incidence of lupus-like syndrome compared with DPA has been described[9]. AE related to trientine are generally mild and include headache, arthralgias, myalgias, nausea, anorexia, diarrhoea, rash, and renal dysfunction[9].

A recent multicentre, randomized, non-inferiority, open label study has evaluated the efficacy and safety of trientine tetrahydrochloride *vs* DPA in patients with stable WD. Fifty-three adult patients with clinically stable disease for more than one year were followed for a 12-week reference period before being randomized 1:1 to trientine tetrahydrochloride or DPA twice daily. The primary endpoint of the

study was to obtain non-ceruloplasmin-bound copper (NCC) levels within the therapeutic range. NCC was assessed with a novel method based on copper speciation. The secondary endpoint was to obtain both NCC and UCE rates within the optimal range. The CHELATE study met its primary efficacy endpoint by demonstrating that trientine tetrahydrochloride was non-inferior to DPA. Five serious AE were observed in the 27 patients treated with DPA, while none were observed in the 26 patients randomized to trientine tetrahydrochloride [NCT03539952]. Trientine tetrahydrochloride is produced as a scored tablet which is stable at room temperature, in contrast with trientine dihydrochloride which is a capsule and needs to be stored in the fridge[28,29].

### Zinc salts

Zinc competes with the uptake of copper in the gastrointestinal mucosa and induces metallothionein synthesis in the enterocyte. Metallothionein binds copper and inhibits its transport into the bloodstream [30]. Moreover, zinc may induce elevated levels of hepatocellular metallothionein, enhancing cellular copper storage capacity[31,32]. The first studies conducted involved zinc acetate, due to the common thought that the alternative zinc agents (*e.g.* sulfate, gluconate) might not be as well absorbed or as effective[7]. However, Camarata *et al*[33] retrospectively reviewed a single centre experience of patients who were on zinc therapy with zinc acetate or with alternative zinc salts and demonstrated that the absorption was good for all types of zinc agents and that they were similarly effective in terms of alanine-aminotransferase normalization and urine copper excretion. Current guidelines recommend against the use of zinc for the treatment of symptomatic WD patients with hepatic manifestations, as it appears to be less effective, although it can be used as first-line therapy in neurologic patients[7]. Zinc can also be used as a maintenance therapy for asymptomatic patients. Cases of disease progression have been reported in patients with hepatic WD treated with zinc[7]. Zinc salts can be used as an alternative treatment for patients intolerant to chelating agents and for the treatment of very young patients[30]. In adults, zinc is usually administered at 150 mg/d divided in 2-3 doses, whereas in children below the age of 15 years the dosage of zinc is of 75 mg/d in 2-3 divided doses[22]. Similarly to DPA and trientine, zinc should not be administered with meals because food interferes with its absorption[34]. The most common AE due to zinc salts are gastric irritation, which develops in about 30% of patients[7], and clinically irrelevant increased serum lipase and /or amylase levels[35]. In addition, zinc can be associated with leukopenia and bone marrow depression[36,37].

### Potential new pharmacological treatments

New treatment options are being studied mainly to reduce the risk of neurological deterioration during treatment or to improve patient compliance. The FOCUS phase III study comparing bis-choline tetrathiomolybdate (TTM) with other standard-of-care anti-copper compounds has been started in 2018. TTM binds to copper to form an inert protein complex that cannot redistribute to the central nervous system and for this reason could be a future treatment option for neurological patients[38]. Sodium 2,3-dimercapto-1-propane sulfonate (DMPS) is an intravenous copper-chelating agent that forms complexes with copper which are excreted by the. In China, DMPS is routinely employed for the treatment of WD. In combination with zinc, it was found to be more effective than zinc alone for the treatment of patients with a history of neurological deterioration during DPA[39]. In a recent retrospective study on 158 patients, the combination of DMPS and zinc was also found to have better results than DPA in neurological WD[22]. To improve adherence in the long term, the possibility of administering a single daily dose of trientine as a maintenance therapy has been explored in a study that included 8 patients who were followed for 12 mo[40,41]. The once daily dosing of trientine seems to improve compliance while maintaining effectiveness[40,41]. Larger trials with longer duration of follow up and testing of dose response are required to assess the safety, long-term efficacy and cost effectiveness of single dose trientine treatment for maintenance therapy in WD. Gene therapy approaches for replacement of the mutated ATP7B have been successful in animal models of WD and remain a potential mean to cure WD [42].

### Vitamin B6

DPA therapy has been associated with biochemical evidence of pyridoxine deficiency. In the literature, only one case of clinically relevant pyridoxine deficiency induced by DPA has been reported. A man, whose nutritional status and therapy regimen were not specified, developed peripheral sensory neuropathy (WD does not affect the sensory nervous system) shortly after having initiated treatment with DPA. The symptoms rapidly cleared with vitamin B6 integration, without DPA discontinuation[43-46]. Epilepsy was initially suggested to be a manifestation of vitamin B6 deficiency in WD patients treated with DPA, but this finding was not confirmed in later studies[47,48]. Since WD patients require a lifelong treatment, a 25-50 mg per os daily pyridoxine supplementation is recommended, albeit in lack of strong evidence[7,9].

### Psychiatric treatment and mental care

There are currently no recommendations for the treatment of psychiatric manifestations of WD, which include personality and mood disorders, cognitive impairment, and psychosis[49]. De-coppering agents

typically lead to an improvement of psychiatric symptoms, but when specific psychiatric treatment is needed, potentially hepatotoxic drugs should be avoided[49]. Clinicians can safely opt for selective serotonin reuptake inhibitors such as escitalopram and citalopram. Valproate should be administered with caution because it could be hepatotoxic. Haloperidol should be avoided as neurological deterioration, including neuroleptic malignant syndrome, was more frequently reported when using this drug; olanzapine, quetiapine, and aripiprazole can be used to treat psychosis. Patients on lithium should be monitored carefully[49].

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## LOW-COPPER DIET

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Studies on healthy individuals have shown that copper absorption is influenced by the copper content of the diet. High dietary copper reduces the efficacy of copper intake into enterocytes. As copper absorption is not affected in WD, these conclusions could be extended to WD patients[50]. Thus, low-copper diets could in fact increase the proportion of dietary copper which is absorbed. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) both recommend a low copper diet, especially in the first year of treatment, based on a consensus of experts[7,9]. This recommendation was supported by a single study by Brewer *et al*[51] on two non-compliant WD patients which had signs of an improved copper metabolism status after having started a lacto-vegetarian diet: in one patient, the daily intake of copper was not reduced (1046 µg), and in the other patient it was not specified. Recommended dietary allowances (RDA) for copper in adults are 900 µg and 1300 µg during pregnancy[52]. A study by Srikumar *et al*[53] showed that switching to a lacto-vegetarian diet, which is generally rich in fibres and phytates, seems to reduce the bioavailability of copper by 25%. Although the first patient in the study by Brewer *et al*[51] consumed fruit and vegetables, the second patient ate fruits but not vegetables, cereals, legumes, and nuts, which are the major dietary sources of fibres and phytates; this makes the causative relationship between diet modification and copper overload improvement less plausible. WD patients should only avoid – or at least eat in very little quantity – the richest dietary copper sources which include shellfish (*e.g.*, oysters which contain 4800 µg/serving of 85 g) and organ meats (*e.g.*, beef liver which contains 12400 µg/serving of 85 g), especially in the first year of treatment. Chocolate, mushrooms and nuts can be consumed in moderation (*e.g.*, 50 g of dark chocolate, one big potato eaten with its skin, 3/4 of a cup of shiitake mushrooms, or 35 g of cashew nuts cover the RDA for copper)[54].

Copper concentrations in tap water vary widely. Results from a number of studies from Europe, Canada, and the United States indicate that copper levels in drinking-water can range from  $\leq 0.005$  to  $> 30$  mg/Litre, with the primary source most often being the corrosion of interior copper plumbing[55]. In the United States, as of 2016, 78% of newly installed utility lines used copper, and it was estimated that 35%-40% of single-family homes newly constructed in 2019 would have had copper piping[56]. For these reasons, it might be sensible to suggest WD patients who mainly consume tap water to measure water copper levels, particularly in case of copper plumbing[55]. Copper containers or cookware without inner lining should not be used to store or prepare foods or drinks, although in lack of studies which demonstrate the amount of copper leaching[9]. Tin-lined copper cookware and containers can be used as they release 0.9-270 µg per kg of food[57].

It must be noted that the only proven therapy for Wilson disease is pharmacological; hence, the clinician should focus more on obtaining compliance to treatment rather than dietary restriction.

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## CLINICAL MONITORING

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Asymptomatic non-cirrhotic WD patients should undergo neurologic examination and abdominal ultrasound (US) annually in order to evaluate disease progression due to poor adherence[58]. Ophthalmologic examination with slit-lamp for Kayser-Fleischer (K-F) corneal rings should be performed until disappearance, and can be requested during follow-up when copper overload due to non-compliance is suspected[59]. At diagnosis, K-F rings are present in almost all neurologic WD patients, 50% of hepatic, and 20%-30% of asymptomatic patients[3]. Elastographic methods could be useful to monitor liver disease evolution[60]. Liver biopsy could be useful during chronic monitoring of patients with WD, as it can discriminate between liver disease due to copper overload (in case of non-response or non-adherence to anti-copper drugs) and alternative diagnoses. Unfortunately, liver copper levels are not routinely assessed; when available, liver copper levels greater than 250 µg/g are suggestive for copper accumulation seen in WD patients. False negatives can be caused by sampling error, especially in advanced liver disease[61]. Long-standing cholestatic disorders are associated with higher hepatic copper content[7]. Although hepatocellular carcinoma seems to be a rare complication of WD, regular US screening is recommended for patients with liver cirrhosis[62,63]. Histological analysis prior to treatment is advisable when a liver lesion is detected in a cirrhotic patient due to an increased risk of intrahepatic cholangiocellular carcinoma[64]. Copper overload reduces bone mineralization; for this reason, WD patients should be screened for osteoporosis, which has been reported in up to 43% of

patients[3].

## BIOCHEMICAL MONITORING

### **Ceruloplasmin**

In patients with WD the incorporation of copper in apo-ceruloplasmin to form holo-ceruloplasmin (which has ferro-oxidase activity) is impaired, and patients generally have low ceruloplasmin levels[7]. Ceruloplasmin is an acute-phase reactant and can be increased in patients treated with oral contraceptives and during pregnancy[7]. In 1970, Holtzman *et al*[65] indirectly measured degradation rates for holo- and apo-ceruloplasmin and supposed that apo-ceruloplasmin was eliminated more rapidly than holo-ceruloplasmin. This widely accepted pathophysiological mechanism which would explain the low levels of ceruloplasmin found in WD patient has been recently questioned by Linder, who used radiolabelled ceruloplasmins and directly quantified the apo- and holo-form, demonstrating that degradation rates could be similar between holo- and apo-ceruloplasmin[1]. Further research is needed to support these conclusions and to find an alternative explanation for hypoceruloplasminemia in WD patients. Linder also suggests that in healthy individuals, half of the circulating ceruloplasmin is in the apo- and therefore copper-free- form, whereas it is commonly believed that 95% of the circulating ceruloplasmin is in the holo-form. Previous findings might have led to some misconceptions about the amounts and variations of "free" copper levels, a serum marker frequently used for diagnosis and monitoring of patients with WD[1]. Linder's conclusions should stimulate further studies to understand the possible implications in patients with WD.

The measurement of ceruloplasmin does not have a role in the monitoring of WD patients, but it is commonly used to estimate NCC.

### **NCC**

NCC is an indirect estimation of the proportion of copper that is not bound to ceruloplasmin, which is believed to be the toxic copper component in WD. Patients with WD have low total serum copper since this measurement includes ceruloplasmin-bound copper, which is deficient in WD patients[66]. In patients treated with DPA and zinc, significant reductions in NCC can be expected after 1 year of treatment. Trientine might lead to a delayed biochemical response[66].

NCC is calculated by multiplying the concentration of holo-ceruloplasmin protein by the percentage of holo-ceruloplasmin mass attributable to copper, and that is subtracted from the total serum copper [NCC = total serum copper concentration (in  $\mu\text{g}/\text{dL}$ ; serum copper in  $\mu\text{mol}/\text{dL} \times 63.5 = \text{serum copper in } \mu\text{g}/\text{dL}$ ) -  $3.15 \times \text{holo-ceruloplasmin in mg}/\text{dL}$ ][7].

This calculation can be misleading as most laboratories do not differentiate between the apo- and holo-form and provide total ceruloplasmin levels as a result. There is evidence that in WD patients holo-ceruloplasmin accounts for 8%-40% of total ceruloplasmin, and that in some patients there can be a complete deficiency of holo-ceruloplasmin, especially when ceruloplasmin levels are very low[1,67]. Holo-ceruloplasmin, the enzymatically active form of ceruloplasmin, ought to be calculated directly by using an enzymatic assay, which unfortunately is only available in specialised centres[68,69]. In the United Kingdom, only 3.4% of laboratories used enzymatic methods for the calculation of NCC whereas in 96.6% of cases the measurement was invalid as ceruloplasmin was dosed with immune-nephelometric assays[68]. Immunologic tests cannot discriminate between the two forms and consequently overestimate holo-ceruloplasmin levels which leads to an underestimation of NCC[7].

When available, a level of NCC between 5-10  $\mu\text{g}/\text{dL}$  and 15-25  $\mu\text{g}/\text{dL}$  is considered as an index of treatment efficacy while avoiding copper deficiency[70,71]. In any case, the results should be integrated with other biochemical and clinical tools to evaluate the copper load, as in a study by Dzieżyc *et al* no statistically significant differences were found in NCC values between compliant and non-compliant WD patients, suggesting that NCC might not be a reliable tool to monitor patients with WD[71].

Finally, different laboratories might produce significantly different results for NCC and therefore patients are strongly suggested to perform routine tests at the same centre[68].

### **Exchangeable copper**

In 2009, El Balkhi *et al*[2] proposed a new assay to quantify unbound serum copper directly, as opposed to NCC which is an estimation. Exchangeable copper (CuEXC) includes copper which is loosely bound to albumin, transcuprein, and low molar mass molecules, and therefore not bound to ceruloplasmin. In a more recent study by Woimant *et al*[72], CuEXC values of untreated exclusively hepatic WD patients were found to be normal or moderately increased except in case of acute liver failure associated with Coombs negative haemolysis. On the other hand, CuEXC seemed to be a good marker of extrahepatic manifestations of WD. Preliminary data presented by Poujois *et al*[73] on 100 patients (whose phenotype was not clearly defined) show that abnormal levels of CuEXC, which were observed in 25% of patients, reflected compliance/observance issues. In 50% of them (12/25), this variation CuEXC was associated with hypertransaminasemia. In mainly neurological WD, CuEXC correlated well with the disease severity score, but this was not true for purely hepatic WD[73]. Further investigations are required to



understand the role of CuEXC in chronic management of hepatic WD. It seems reasonable to assume that levels of CuEXC below 0.62  $\mu\text{mol/L}$  could be a sign of overtreatment, whilst CuEXC above 1.15  $\mu\text{mol/L}$  could be a sign of non-compliance[73].

### **Relative CuEXC**

Relative CuEXC (REC) corresponds to the ratio CuEXC/total serum copper. A REC value of 18.5% appeared as an excellent biomarker for the diagnosis of WD, with 100% sensitivity and specificity[73]. The possible role of REC in chronic management of WD has not been investigated.

### **UCE**

UCE rate reflects copper overload and is the most valuable and widely available tool to monitor patients with WD[66]. A UCE rate of over 100  $\mu\text{g}/24\text{ h}$  is considered typical for symptomatic WD and levels over 40  $\mu\text{g}/24\text{ h}$  can be suggestive for asymptomatic WD[7,66]. After starting treatment with chelators, there is an increase in UCE with a peak at 6 and 18 mo for DPA and trientine, respectively. In the long-term, UCE rates tend to decrease and stabilise, not necessarily at lower rates than those detected at treatment initiation. UCE rates are higher in patients treated with DPA compared with trientine but do not differ with respect to the type of clinical presentation of the disease[66]. In case of renal failure, this test is not applicable. In patients treated with DPA and trientine, the UCE should not be lower than 200 (which could be a sign of overtreatment) nor greater than 500  $\mu\text{g}/24\text{ h}$ , although higher values are frequently found in compliant patients[71] and therefore this UCE goal range might need to be redefined. Increased urinary copper levels are detected in non-compliant patients who start taking drugs just before the assessment[71]. Zinc therapy reduces copper absorption and does not increase UCE rates: the treatment target should be to obtain UCE values of 20-50  $\mu\text{g}/24\text{ h}$  at least 2 years after treatment initiation[7,66,74]. During treatment with zinc, if UCE falls below 40  $\mu\text{g}/24\text{ h}$  possible overtreatment should be anticipated, and zinc dosage should be reduced[7,74]. Copper overload due to non-adherence to zinc therapy should be suspected when UCE rates increase to over 100  $\mu\text{g}/24\text{ h}$  during follow up. Non-compliance to zinc can be easily detected by measuring urinary zinc excretion that should not be below 2 mg/24 h[75].

In brief, UCE is influenced by the type of medical therapy, patient age (older patients have lower UCE), length of dose interruption before UCE measurement, and duration of medical therapy. UCE rates have great interindividual variability so each patient's previous results should be used as a reference[66].

### **UCE after 48 h of DPA cessation**

A useful tool to detect non-compliance is the measurement of UCE after 48 h of DPA cessation. The optimal cut-off to identify compliant patients was found to be 49  $\mu\text{g}/24\text{ h}$ . This test has a high specificity (87%) but a lower sensitivity (77%), thus we cannot exclude non-compliance even if the test comes out negative[71]. UCE rates in non-compliant patients who do not even take DPA just before the assessment would supposedly be over 49  $\mu\text{g}/24\text{ h}$  but not as high as with the chelator stimulus. UCE after 48 h or DPA cessation was found to be significantly reduced after 1 year of treatment, as opposed to UCE measured without treatment discontinuation[66]. This finding suggests that UCE after 48 h of DPA cessation might be more useful than UCE without DPA interruption for chronic monitoring of WD patients.

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## **OVERALL CONSIDERATIONS ON CHRONIC MONITORING OF PATIENTS WITH WD**

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The copper metabolism tests are not standardised and have many limitations which may hinder the diagnostic process of WD: urinary copper levels can be increased in cholestatic liver diseases; in malnutrition or malabsorption serum ceruloplasmin levels can be below normal values; the classic triad of low serum ceruloplasmin, low serum copper and high UCE can be present in 15% of heterozygote carriers[72]. Nevertheless, if these tests are used to monitor patients with an established diagnosis, they may be less confounding, as each result can be compared to previous measurements[71]. Patients with urine copper excretion which varies greatly among different measurements – with or without elevated transaminases – might not be compliant. Patients with progressively lower NCC/CuEXC and lower urine copper levels could be overtreated. Each laboratory result should be registered to identify individual trends and physicians should always search for clinical or biochemical signs of overtreatment or of active WD. Non-response can be suspected, as an alternative to non-compliance if clinical manifestations of WD do not improve with treatment. In asymptomatic or compensated WD patients, non-adherence generally leads to recurrence or appearance of clinical or biochemical signs of the disease. Practical suggestions to interpret WD workup are summarised in [Figure 1](#). The main clinical manifestations of WD, overtreatment, and AE related to anti-copper drugs are reported in [Table 1](#).

In a study by Iorio *et al*[76], 20% of patients had persistent hypertransaminasemia without evidence of disease progression: in such cases, it is most important to carefully assess the patient's compliance, alternative aetiologies, and disease progression (possibly even with a liver biopsy). Once compliance has

**Table 1 Clinical manifestations of Wilson's disease, copper deficiency, and anti-copper drugs adverse events**

Clinical manifestations		
Wilson's disease	Copper deficiency	Anticopper drugs adverse events
Cardiac disturbances	Cardiac disturbances	<b>D-penicillamine</b> (20%-30%)
Arrhythmia (atrial fibrillation)	Severe bradycardia	Alopecia
Autonomic disturbances	Cutaneous manifestations	Arthralgias/arthritis
Cardiomyopathy	Cutaneous defective keratinization	Degenerative dermatoses (cutis laxa, anetoderma caused with focal loss of elastic tissue, pseudoxanthoma elasticum, elastosis perforans serpiginosa)
Cutaneous and subcutaneous manifestations	Decubitus wounds	Cephalgia
Acanthosis nigricans	Delayed wound healing	Eryhema
Anetoderma	Depigmentation of the skin and hair	Fatigue
Azure lunulae of the nails	Hematologic disturbances	Hematuria
Dermatomyositis	Anemia (microcytic, normocytic, or macrocytic)	Hirsutism
Hyperpigmentation of the legs	Leukopenia	Hypogeusia
Lipomas (multiple, mainly affecting trunk and extremities)	Pancytopenia	Increase of antinuclear antibodies
Xerosis	Thrombocytopenia (rare)	Leukopenia or bone marrow depression
Endocrine system manifestations	Neurologic involvement	Lupus erythematosus
Amenorrhea	Myelopathy or myeloneuropathy (spastic paraparesis or tetraparesis or spastic ataxic gait)	Myalgias
Growth disruption	Progressive optic neuropathy (unilateral or bilateral)	Nausea
Infertility		Paradoxical neurological worsening
Parathyroid failure		Proteinuria
Recurrent abortions		Pruritus
Hematologic disturbances		Sicca symptoms
Acute Coombs-negative hemolytic anemia		<b>Trientine</b> (5%-10%)
Leucopenia, anemia, and low platelet count		Arthralgias
Hepatic involvement		Eryhema
Acute liver failure		Hirsutism
Chronic hepatitis		Increase of antinuclear antibodies
Hepatocarcinoma		Leukopenia
Intrahepatic cholangiocellular carcinoma		Lupus erythematosus
Liver cirrhosis		Myalgia
Steatosis		Nausea and/or diarrhoea
Neurological manifestations		Paradoxical neurological worsening
Dysarthria		Pruritus
Dysphagia		Sideroblastic anemia
Dystonia		<b>Zinc salts</b> (3%-7%)
Gait disturbance		Gastritis
Risis sardonicus		Increase in amylase and/or lipase (with no clinical relevance)
Rigidity		Leukopenia and bone marrow suppression

Tremor
Less frequent manifestations: chorea, athetosis, seizures and pyramidal signs
Ophthalmologic signs
Degeneration of retina and optic nerve
Kayser-Fleischer corneal rings
Sunflower cataracts (rare, not associated with ipovivus)
Osteoarticular involvement
Arthropathy (affecting mainly knees and wrists)
Osteopenia and osteoporosis
Skeletal abnormalities
Renal involvement
Elevated levels of blood urea nitrogen, creatinine, and uric acid (not associated with renal impairment)
Urinary calculus

Therapeutic goals			Overtreatment			Non-compliance/non-response		
NCC <sup>1</sup> = 5-25 µg/dL			NCC <sup>1</sup> < 5 <sup>2</sup> /10 <sup>3</sup> µg/dL			NCC <sup>1</sup> > 25 <sup>2</sup> /15 <sup>3</sup> µg/dL		
No clinical manifestations of WD or Cu deficiency			Clinical manifestations of copper deficiency			Clinical manifestations of WD		
Zinc	DPA	Trientine	Zinc	DPA	Trientine	Zinc	DPA	Trientine
UCE = 20-50 µg/24 h	UCE = 200-500 µg/24 h	UCE = 200-500 µg/24 h	UCE < 20 µg/24 h	UCE < 200 µg/24 h	UCE < 200 µg/24 h	UCE = 20-50 µg/24 h	UCE > 500 µg/24 h <sup>4</sup>	UCE > 500 µg/24 h
UZE > 2 mg/24 h	DPA CT = 20-50 µg/24 h		UZE > 2 mg/24 h	DPA CT < 20 µg/24 h		UZE < 2/> 2 mg/24 h <sup>5</sup>	DPA CT > 50 µg/24 h	

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**Figure 1 Broad guidance for Wilson’s disease workup interpretation.** <sup>1</sup>Only valid if holo-ceruloplasmin is calculated with an enzymatic test. <sup>2</sup>Higher probability/<sup>3</sup>Lower probability of overtreatment or non-compliance. <sup>4</sup>Non-compliant patients who take DPA on the day of the 24 h urinary collection; UCE in non-compliant patients who do not take DPA > 48 h prior to the assessment should be interpreted as D-penicillamine 48 h cessation test results. <sup>5</sup>UZE < 2 mg/24 h in non-compliance/UZE > 2 mg/24 h in non-response. DPA: D-penicillamine; DPA CT: D-penicillamine 48 h cessation test; NCC: Non-ceruloplasmin-bound copper; UCE: Urinary copper excretion; UZE: Urinary zinc excretion.

been demonstrated, other aetiologies have been ruled out, and disease progression is not documented, persistent hypertransaminasemia can be considered harmless, although further studies are warranted to confirm this result.

At treatment initiation, patients should be evaluated frequently so as to ensure clinical and biochemical improvement, allow dose adjustments, and identify early side effects of anti-copper drugs. During chronic monitoring patients should be assessed once or twice a year, depending on the clinical status and on compliance. A suggested protocol for chronic monitoring of patients with WD is presented in [Table 2](#).

Adulthood hepatologists should acknowledge that adolescents and young adults are at higher risk for non-adherence. Long duration of treatment and asymptomatic periods during chronic disease also create poor compliance; hence, after transition from paediatric care, when patients start taking their medications without parent supervision, medical counselling should focus on increasing the individual’s perception of vulnerability to disease and its consequences, as it is an important determinant for good compliance[77].

A useful tool to assist patients and physicians in tracking Wilson disease treatment and monitoring history has been provided by the WD association (<https://www.wilsons-disease.org/for-patients->



**Table 2 Suggested clinical and biochemical chronic monitoring of patients with Wilson's disease**

Clinical and biochemical monitoring of Wilson's disease	
Clinical monitoring	Biochemical monitoring
Abdominal US (1/yr in non-cirrhotic, 1/6 mo in cirrhotic patients)	NCC = total serum copper concentration (in µg/dL; serum copper in µmol/dL × 63.5 = serum copper in µg/dL) - 3.15 × holo-ceruloplasmin in mg/dL
Neurological assessment (using the Unified Wilson's Disease Rating Scale) at every follow-up visit	24-h urine copper excretion
Identification of possible side effects of anti-copper drugs	Liver enzymes and liver function tests (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl-transferase, alkaline phosphatase, bilirubin, international normalized ratio, and albumin) creatinine, and complete blood count
Gastroscopy in cirrhotic patients, when appropriate	<b>For patients treated with DPA and trientine:</b> 24 h-urine protein test, anti-nuclear antibodies
Transient elastography (1/yr in non-cirrhotic patients)	<b>For patients treated with zinc:</b> 24-hour urine zinc excretion
Central bone density scan at diagnosis, then individualise follow-up	
<b>If non-compliance is suspected:</b> Slit-lamp examination to search for Kayser-Fleischer rings, brain MRI	
<b>For patients treated with DPA:</b> skin biopsy at 10 yr from treatment initiation	

DPA: D-penicillamine; MRI: Magnetic resonance imaging; NCC: Non-ceruloplasmin-bound copper; US: Ultrasound.

[families/Lab-tracker-copper-calculator](#)).

## PREGNANCY

Since WD is diagnosed in the early decades of life, pregnancy can often be part of the life of a woman with WD. First of all, preconception genetic counselling should be offered to all patients with WD, as it is an autosomal recessive disease and heterozygous carrier frequency has been reported to be as high as 1/31 subjects in a large cohort study in France[11]. Secondly, clinicians should aim at obtaining clinical stability before conception in order to improve the chances of having a successful pregnancy. Knowledge on pregnancy in WD had been previously gathered through small case series and reports [78], until 2017, when Pfeiffenberger *et al*[79] conducted a retrospective, multicentre study analysing 282 pregnancies over 40 years. Miscarriage rates were significantly higher in patients with undiagnosed – and therefore untreated – WD patients compared with treated women (40.7% in untreated women *vs* 10% in patients treated with zinc and 17% of women treated with DPA)[79]. In this study, 6% of patients experienced a worsening of liver function tests during pregnancy, regardless of whether they were on treatment or not. These test abnormalities resolved after delivery. Fourteen patients discontinued treatment during pregnancy without experiencing a deterioration of hepatic or neurologic symptoms, although the Authors do not suggest interrupting treatment during pregnancy[79]. Current AASLD guidelines suggest maintaining zinc therapy at regular dosage and reducing the dosage of chelating agents by 25%-50%, as copper deficiency at delivery might impair wound healing[9]. EASL guidelines advocate that there is not enough evidence to support dose reduction during pregnancy[7]. Kodama *et al*[80] found undetectable chelating drug levels in breast milk of mothers with WD and normal copper levels, suggesting that trientine and DPA could be safely administered during breast-feeding. Breast milk zinc levels were found to be higher in patients treated with zinc compared with controls, although all infants (19/19) of woman treated with chelating drugs or zinc were born normally and exhibited normal development even if treatment was maintained during lactation[80]. Finally, pregnant women with WD should undergo frequent check-ups in order to give clinicians the possibility to intervene in case of over/undertreatment.

## PROGNOSIS

In a large cohort study by Beinhardt *et al*[81] which comprised patients predominantly presenting with hepatic symptoms and treated with DPA, the overall age- and sex-matched survival rates in WD

patients 20 years after the diagnosis were not significantly worse than those of the healthy population (0.92 *vs* 0.97; log-rank:  $P = 0.03$ ). In contrast, life expectancy was substantially lower when cirrhosis was present at diagnosis (0.84 *vs* 0.97, log-rank:  $P = 0.008$ )[66]. A minority of patients required liver transplantation (12%) up to 23 years after diagnosis. Adherence was not assessed in this study. In asymptomatic patients, compliance to treatment may lead to normal survival rates and prevent neuropsychiatric symptoms and fatal liver failure[69]. Low adherence to medical treatment has been estimated between 25% and 45% in WD patients; thus, identifying non-adherence and obtaining compliance should be the main objectives of clinicians who treat WD patients[73].

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## CONCLUSION

WD is rare but potentially curable; treating patients with WD can be challenging as copper metabolism tests still have not been standardised. This review aims at providing clinicians with a broad guidance on interpretation of disease workup and on chronic management of patients with asymptomatic and hepatic WD. In addition, it provides an analysis of available evidence on pregnancy and breastfeeding and on the role of copper-restricted diet in WD. The possibility of incomplete penetrance in WD patient warrants further investigation.

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## FOOTNOTES

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