Chapter 3
Treatment Options for Wilson Disease

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Treatment Options for Wilson Disease

Once a diagnosis of Wilson disease (WD) is established, treatment is needed. Treatment includes medical therapy directed at reducing the excess copper in the liver and other organs but also aimed at reducing symptoms of disease arising due to damage of the liver, brain, or other organs. Treatment also includes dietary management, physical or speech therapy if needed, or other interventions that try to enhance the quality of the patient's life. In those in

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whom medical therapy is not possible due to liver failure or whom fail medical therapy, liver transplantation can be curative.

Treatment of patients diagnosed with WD can be divided into different stages and also has situations where there are special considerations:

1. *Initial therapy* that aims to remove excess copper from newly diagnosed symptomatic patients or *initial therapy* that aims to prevent signs and symptoms of disease in pre-symptomatic patients.
2. *Maintenance therapy* begins when stability of copper metabolism and symptomatic and continues lifelong.
3. Liver transplantation when medical therapy doesn't or will not work.
4. Other special circumstances: pregnancy and surgery (discussed in chapter 10).

Successful treatment of patients with WD requires a global view of the patient and the state of their disease, and for complex patients a multidisciplinary approach is often needed to achieve best outcomes. This chapter will focus mainly on drug therapy aimed at controlling the disordered copper metabolism which is the basis of this disorder but also on liver transplantation and when it is indicated. Treating other potential complications of WD, including those resulting from advanced liver disease, effects on the brain (neurologic and psychiatric disease), as well as dietary therapy to reduce intake and address nutritional needs that are important for overall health are addressed elsewhere in this book.

Drug therapy for WD was initially introduced in the 1950s, but the relatively rare nature of this condition and the manner in which the initial treatments were introduced (without dose-ranging studies, strict pharmacokinetic analysis, and head-to-head comparison studies between treatments to know which is best or safest) have left gaps in our knowledge of how best to use the currently available treatment regimens. Indeed, the choice of treatment for WD is often based on preferences of the treating physician or patient and may be guided by other factors (e.g., insurance coverage) as well as variable access to specific medications rather than by any available studies showing superiority of one treatment over another.

How then is a patient to choose between treatments? A working knowledge of the available medications and treatment options is the responsibility of the specialist who is prescribing the medications, but given the rarity of the disorder, it is likely that in any one community, there are not many treating physicians with experience. Patients and caregivers are therefore encouraged to learn more about their treatment options themselves and to seek further consultation at centers of excellence (designated by the patient-run Wilson disease Association, https://www.wilsonsdisease.org) where expert multidisciplinary teams are able to provide comprehensive consultation and make recommendations that incorporate the latest information, including participation in clinical trials.

A summary of the available oral therapies is shown in Table 3.1.

Drug Therapy

Dimercaprol (British Anti-Lewisite, BAL)

Dimercaprol (British anti-lewisite, BAL) was the first drug that successfully treated WD and provided dramatic improvement in patients with neurologic symptoms due to WD in whom no prior treatment was available. Recordings of some of the incredible responses to the treatments with this therapy are available [1]. BAL chelates (binds) and then causes

Table 3.1 Oral therapy for Adults with WD

Treatment	Dosing regimen	Mode of action
D-penicillamine	Usually 750–1000 mg in 3–4 divided doses	Chelator promoting urinary excretion of copper
Trientine	Usually 1000–1500 mg in 2–3 divided doses	Chelator promoting urinary excretion of copper
Zinc salts (gluconate, sulfate and acetate)	150 mg elemental zinc in three divided doses	Reduces copper absorption

removal of copper in the urine. This drug is rarely used now as it requires regular intramuscular injection and may cause a systemic hypersensitivity reaction and local sterile abscesses at the injection sites. The oral chelators D-penicillamine and trientine, discussed next, were developed in a bid to overcome the problems associated with BAL. A summary of the characteristics of these oral medications is shown in Table 3.2.

Table 3.2 Characteristics of commonly used therapies in adults for WD

Treatment	Advantages	Disadvantages
D-Penicillamine	Lengthy clinical experience Data supporting use Suitable for all presentations of WD	Frequency of side effects Hypersensitivity (fever and rash) Requires supplemental pyridoxine Marrow suppression Paradoxical neurological worsening during initiation of treatment Lupus-like syndrome Skin changes Colitis[a] Frequency of dosing
Trientine	Less side effects than D-penicillamine Suitable for all presentations of WD	Needs to be kept refrigerated Sideroblastic anemia Paradoxical neurological worsening during initiation of treatment Hemorrhagic gastritis[a] Duodenitis[a] Loss of taste Rash
Zinc salts	Well tolerated Neurological deterioration is uncommon	Gastrointestinal side effects Elevated lipase and/or amylase[a] Frequency of dosing Unclear if safe as monotherapy in hepatic disease

[a]Rare events

D-Penicillamine

D-Penicillamine was first used in WD in 1956 [2]. It acts by binding the copper and increasing its urinary excretion, but it may also induce metallothionein (a naturally occurring peptide that can safely bind copper) in the liver [3]. D-Penicillamine was shown to be useful in treating WD in many clinical studies [4–11]. In patients with liver disease, recovery of synthetic function of the liver and improvement in signs and symptoms related to WD can be seen in the initial 2–6 months of treatment, with even further recovery possible during the next year and beyond. There are even reports of advanced fibrosis (scarring in the liver) and cirrhosis improving on prolonged therapy [12]. In patients with neurologic WD, improvement of symptoms is often slower and may continue for a few years [6].

To improve tolerability, it is recommended to start with a low-dose regimen initially and slowly increase the dosage; starting with 125–250 mg/day that is increased by 250 mg every 4–7 days to a maximum of ~1500–2000 mg/day in 2–4 divided dosages in adults or to ~ 20 mg/kg in children. If taken with food, absorption of D-penicillamine is decreased [13], and therefore it is recommended to take this medication 1 h before or 2 h after meals. For children who cannot swallow capsules or for those with severe neurologic impairment and have difficulty swallowing and have either a gastric feeding tube or naso-enteral feeding tube, D-penicillamine is available in a liquid formulation. After successful treatment for a period of ~ 6–12 months during which time most excess circulating copper has been removed (see monitoring chapter for details of testing to follow while on treatment), the dose of D-penicillamine can be reduced by about 30–15% mg/kg for those who continue on D-penicillamine for maintenance therapy. Additionally, D-penicillamine interferes with vitamin B6 action; therefore supplemental pyridoxine should be provided (25–50 mg/day) as well to WD patients on D-penicillamine therapy.

While the majority of WD patients do well on treatment with d-penicillamine, unfortunately, worsening of neurologic symptoms may occur in some who are started on

D-penicillamine during their initial phase of treatment [6] or who restart this medication after long gaps in therapy. This neurological worsening is not unique to this drug and has been reported for other treatments used for WD, but it may be more frequent with D-penicillamine [14]. It is thought that worsening of neurologic symptoms or appearance of new neurologic symptoms following the initiation of WD treatment may be related to the mobilization of copper from sites within cells to the circulation given that the chelator-bound copper is still bioactive. However, it is important to remember that neurologic symptoms will certainly progress without treatment, and therefore the benefits of therapy outweigh risks. To reduce the risk of this occurring, many experts recommend a slow ramping up of the dose of D-penicillamine over a period of 1–2 months' time. Although some patients that do develop worsening of their neurologic status recover with continued use of D-penicillamine, it is recommended that the medication be stopped, or at least the dosage decreased when this occurs. There is a lack of clear evidence as to what is the best next step if neurological worsening occurs on treatment. One option is to consider changing treatment to include both zinc and a reduced dosage of chelating drug in combination (but given apart from each other, discussed below).

Another problem with D-penicillamine is the frequent occurrence of side effects, which leads to a change in treatment in around 25% of WD patients [7]. Side effects that are seen early on in treatment include hypersensitivity with fever and rash, marrow suppression, and, as noted above, early paradoxical neurological worsening. Other reactions include a lupus-like syndrome (rash, fever, kidney dysfunction), development of isolated kidney dysfunction with nephropathy (severe protein loss), a Wegener-like syndrome (inflammatory granulomas in the lung and other tissues), myasthenia gravis with muscular dysfunction, as well as dermatological changes including a keloid-like scar known as elastosis perforans serpiginosa and rarely colitis. In general, many of the side effects due to penicillamine are reversible when patients are changed to alternative therapies, trientine or zinc.

Copper-deficient states induced by high-dose D-penicillamine or prolonged treatment on standard dosages in those with strict restrictions of dietary copper. Overtreatment and a copper-deficient state can lead to iron overload in the liver and fatty change in liver cells, and this may contribute to liver injury independent of copper.

Trientine

Trientine is another copper chelator that was introduced in the late 1960s as an alternative to D-penicillamine for patients who could not use this drug. There is published evidence on the use of trientine, but clinical experience has outpaced this, with both suggesting trientine is as effective as D-penicillamine [7, 15–17]. Trientine seems to have fewer side effects and is useful in patients who are intolerant of D-penicillamine or where intolerance is more likely (history of renal disease, splenomegaly with severe thrombocytopenia, autoimmune tendencies) as well as for first-line therapy including in those with decompensated liver disease [18, 19].

The usual initial dose in adults is 20 mg/kg per day, rounded to the nearest 250 mg, given in two or three divided doses, with typical dosages of 900–2700 mg/day, with 900–1500 mg/day used for maintenance therapy in divided doses. The drug should be taken 1 h before or 2 h after meals. Trientine is not stable at high temperatures and should be refrigerated.

Trientine has few side effects. Neurological worsening with treatment initiation is seen with trientine but appears to be less common than with D-penicillamine [20]. No hypersensitivity reactions have been reported, but there is case reporting of a cutaneous drug reaction. Pancytopenia has rarely been reported. Lupus-like reactions have been reported, but almost all of these had previously had D-penicillamine. Rarely, trientine may cause hemorrhagic gastritis, colitis, duodenitis, loss of taste, and rash.

A reversible sideroblastic anemia has been described in case reports possibly because of the effects of trientine on

iron metabolism [21, 22]. Trientine chelates iron, and this trientine-iron complex is nephrotoxic; thus iron supplementation should be avoided. Copper deficiency as a result of high-dose trientine over time can lead to iron overload in the liver, as is also seen with D-penicillamine [23].

Zinc

Zinc was found to be effective WD treatment in the early 1960s [24–27]. It works differently to the chelators described above. It interferes with the uptake of copper from the gastrointestinal tract through enterocyte metallothionein which binds copper, inhibiting its entry into the portal circulation [28, 29]. Once bound, the copper is lost as enterocytes are shed [6]. As copper also enters the gastrointestinal tract from saliva and gastric secretions, zinc treatment can generate a negative balance for copper and so remove stored copper [30].

Experience of zinc in the treatment of WD was gained through maintenance therapy after initial chelator use [31]. It has, however, been used as the initial treatment in patients who developed worsening neurologic symptoms with D-penicillamine, during pregnancy, in young children and in presymptomatic patients [5, 24, 25, 30–39]. The role of zinc in hepatic disease is controversial with conflicting reports over its efficacy. Deterioration has been reported, which proved fatal in one case [40, 41], but other reports suggest equivalent outcomes as is seen with D-penicillamine [42].

It has been suggested zinc may have a role as first-line therapy in patients with neurologic disease as there is no paradoxical worsening; however as it takes longer to reduce copper levels, the disease may progress on therapy. Thus, current guidelines recommend that all symptomatic patients diagnosed with WD should receive a chelating agent (D-penicillamine or trientine) [43, 44].

In presymptomatic patients, zinc is as effective as penicillamine but has less side effects [5].

Zinc is prescribed as zinc salts, with the common salts used being zinc sulfate, acetate, and gluconate. Zinc is dosed as

milligrams of elemental zinc to allow consistent dosing across the different salts used though absorption of each may differ. The recommended dose in adults is 150 mg elemental zinc/day administered in three divided doses, 30 min before food. Taking zinc with food that contains phytates (a component of many grains in bread and cereals) interferes with absorption (a component of many grains in bread and cereals) [45]. Compliance with the three times per day dosage can be an issue, with twice daily still effective, but once daily is not [24]. Zinc has few side effects, with gastrointestinal issues the commonest which may be dependent on the salt employed with acetate and gluconate probably more tolerable than sulfate, but this varies with individuals. Elevations in serum lipase and/or amylase may occur, without clinical or radiologic evidence of pancreatitis. Neurological deterioration is uncommon with zinc [5, 46]. It is uncertain whether zinc is safe for patients with renal dysfunction.

Combination Therapy: Chelator and Zinc

The use of a combination of chelation therapy along with zinc (given separately) can be considered with the different mechanisms of action (preventing copper absorption and removal of excess copper, respectively) felt to have an advantage over either treatment alone.

Patients who present with decompensated cirrhosis have been treated with D-penicillamine [19, 47] or trientine [48], plus zinc. The chelator and zinc must be spread out throughout the day with usually 5–6 h between administrations of either drug, in order to avoid having the chelator bind the zinc. Typically zinc (50 mg elemental adult) is given as the first and third doses and trientine (500 mg) as the second and fourth doses. This is an intense treatment regimen in unwell patients which some will not respond to or tolerate [19, 47, 48]. Therefore, it is important these patients are treated in conjunction with a transplant center. Those who respond may be transitioned to full-dose zinc or full-dose trientine (or D-penicillamine) as monotherapy after 3–6 months. The com-

bination of D-penicillamine and zinc may increase the risk for development of sideroblastic anemia.

Liver Transplantation

Liver transplantation may be the only option for patients who present with acute liver failure (occurs in ~5% with WD) and in those with decompensated liver disease who do not respond to medical therapy [49–54].

Patients with acute liver failure due to WD can have suggestive lab results including an aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio >2.2, an alkaline phosphatase to bilirubin ratio <4, hemolytic anemia, and elevated serum copper >200 mcg/dL. These excess copper ions contribute to the hemolytic anemia.

Patients require treatment and stabilization in ICU and may well require urgent liver transplantation. Rapid removal of excess copper in the blood is crucial, and given the time for decoppering through drug therapy, various alternative methods have been used including hemodialysis, hemofiltration, albumin dialysis, plasma exchange, and molecular adsorbent recirculating system (MARS). A thorough workup for liver transplantation can occur in parallel with ICU care.

Transplantation corrects the hepatic metabolic defects of WD [55], and so patients do not require WD-specific treatment posttransplantation. While the posttransplantation outcomes for liver disease are excellent, transplantation is not recommended as a primary treatment for neurologic WD because any liver disease in these patients is stabilized by medical therapy, and outcomes with liver transplantation are not always beneficial [50, 54, 56–59]. Liver transplant assessment is covered in more detail in chapter 11.

Assessment of Therapy

An important assessment in the treatment of WD is 24-h urine copper excretion (see Table 3.3) which changes in pro-

Table 3.3 Typical results seen in monitoring of therapy in WD

	24-h urinary Cu	NCC (calculated)
Healthy individuals	20–50 μg/day	5–15 μg/dL
Untreated WD	100 μg/day (or greater)	Elevated (>25 μg/dL)
Penicillamine therapy (optimized)	200–500 μg/day	5–15 μg/dL
Trientine therapy (optimized)	200–500 μg/day	5–15 μg/dL
Zinc therapy (optimized)	<100 μg/day	5–15 μg/dL
Overtreated WD	<100 μg/day (chelators) <20 (zinc)	Very low
Poor compliance with therapy	<200 μg/day	Elevated (>25 μg/dL)

portion to the tissue stores depending on whether chelation or zinc therapy is used. Patients taking D-penicillamine or trientine should have 24-h urinary copper excretion values of 200–500 μg/day (3–8 mol/day); for patients on zinc, it should be <100 μg/day (1.2 mol/ day).

For patients on chelation therapy, elevated values for urine copper may suggest nonadherence to treatment. This is particularly important as lack of compliance with treatment leads to significant progression of liver disease and potentially liver failure within 1–12 months following discontinuation of treatment.

Adjunctive Therapy

Some authorities consider the use of other compounds in the treatment of WD. They can be used in conjunction with the therapies outlined above. They are not recommended in US or European guidelines due to a lack of clinical trial data supporting their use.

Curcumin

Curcumin is a naturally occurring compound in the spice turmeric. It could be helpful in WD through its antioxidant properties and may also have a role in copper chelation [60]. There is also experimental work looking at whether curcumin could have capacity to help increase the levels of protein expressed by the ATP7B gene and therefore improve copper export from cells [61]. There is not yet any data to support the clinical use of this compound, but some clinicians add it in to therapy after an individualized assessment.

Vitamin E

Vitamin E is an antioxidant. It has been found to be low in the blood and liver in patients with WD [62]. There have been reports of individuals improving symptomatically with supplementation, but there have also been reports of no correlation with low vitamin E and symptomatology. Therefore, its role is yet to be elucidated in the treatment of WD.

Chinese Herbal Medications

Various Chinese herbal medications (CHM) have been used in the management of WD, both alone and in conjunction with the therapies described earlier. A systematic review of nine randomized trials of varying quality of these medications found the evidence was not sufficient to make a clinical recommendation on their use [63].

Unmet Needs in Treatment of WD

There may be the opportunity to participate in clinical trials in discussion with a WD specialist due to unmet needs in the treatment of this condition.

Treatment can still take time (years) to improve symptoms and this can be compounded by worsening of neurologic symptoms seen in early treatment with existing chelators. A new formulation

of tetrathiomolybdate (TTM) (bis-choline) which acts as first-in-class copper-protein-binding molecule is being investigated, with phase 2 data and extension phase reported [64, 65]. This compound was well tolerated and seems to be promising in addressing the paradoxical worsening of neurologic symptoms seen with other chelators. Phase 3 work is now underway (NCT03403205).

Patients can experience side effects on therapy which can impact on compliance, along with the multiple-dosing regimen of the currently available drugs. Clinical trials are ongoing to try to address these issues. The novel compound TTM described above also confers the advantage of once daily administration. Similarly, there are also trials in once daily administration of trientine [66].

There are issues regarding the affordability of existing therapy. This has led to attempts to develop biosimilar drugs. These are highly similar medicines to others already approved and have the same pharmaceutical quality, safety, and efficacy. Currently there is a clinical trial involving a biosimilar for trientine (EudraCT Number: 2016–003876-29).

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