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Tremor and Other Hyperkinetic Movements

Reviews

Advances in Treatment of Wilson Disease

Annu Aggarwal[1*] & Mohit Bhatt[1]

[1] Wilson Disease Clinic, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India

Abstract

Background: Wilson disease (WD) is an inherited neurometabolic disorder that results in excessive copper deposition in the liver and the brain, affecting children and young adults. Without treatment the disease is invariably fatal. Though treatments for WD have been available since the 1950s, the disease continues to be associated with considerable morbidity and mortality because of missed diagnosis, and delayed or inadequate treatment. In this paper we survey WD-related literature in order to review recent advances in WD treatment.

Methods: We performed a literature search using the PubMed database for articles relating to WD and its medical treatment. We reviewed the articles, and cross-references of relevant articles, to summarize the current practices for treatment of WD.

Results: The survey shows that if WD is properly treated, in most patients the liver can be stabilized, even severe neurological disability reversed, and patients can resume normal lives.

Discussion: Medical treatment for WD includes use of copper chelators (penicillamine, trientine, dimercaprol, dimercaptopropane sulfonate, and ammonium tetrathiomolybdate) and drugs that decrease gastrointestinal copper absorption. Our knowledge of the treatment approaches has benefited from the large systematic clinical studies that have been conducted over the last decade. For each drug used to treat WD, we surveyed its development, indication for use, dosing, efficacy, and adverse effects.

Keywords: Wilson disease, dimercaprol, penicillamine, trientine, zinc, tetrathiomolybdate

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*To whom correspondence should be addressed. E-mail: annu.aggarwal@gmail.com

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Introduction

Wilson disease (WD) was first described by S.A.K. Wilson, in 1912, as a new syndrome of familial lentiform degeneration and liver cirrhosis, which was invariably fatal.[1] For nearly half a century thereafter, the cause of the disease remained unclear and patients continued to die without definitive treatment. Things changed rapidly once John Nathaniel Cumings demonstrated that WD resulted from excessive copper deposition in the liver and the brain.[2] This finding immediately suggested copper chelation as a treatment. The first copper chelator used was intramuscular dimercaprol, which not only increased urinary copper excretion but also resulted in remarkable clinical improvement.[3–5] However, it was soon realized that dimercaprol was not a tenable long-term treatment option as it was associated with considerable adverse effects, rapid drug tolerance, and waning clinical benefits. It was penicillamine, introduced by John Walshe in 1955, that changed the prognosis for WD, making survival as well as dramatic and sustained clinical recovery possible. Subsequently, other effective medical treatments were introduced, and liver transplant became an option for patients with life-threatening liver failure or those who were intolerant to medical treatment.[6,7]

WD was the first of a number of neurometabolic diseases that are now treatable. However, monitoring and titrating treatment of WD remains complex, and the disease is still associated with considerable disability and even deaths due to delayed diagnosis and inadequate treatment. Significant reasons for this are the disease's rarity (prevalence of one in 30,000), multisystemic involvement, and clinical heterogeneity, which make it difficult for a single practitioner to develop sufficient expertise to diagnose and treat WD through

clinical experience alone.[8] The disease's rarity also makes large and comparative clinical trials of WD and its treatment prohibitive, and most studies involve a handful, or a few tens, of subjects (only over the last decade have larger trials with 100+ subjects become somewhat more common). Therefore it is of value to pool the knowledge gained through studies at the numerous clinical and research centers across the world, and disseminate it to medical practitioners who can then apply it in treating WD patients.

In this article, we review and summarize the current treatments available for WD. We focus on definitive medical treatments that directly address the root issue of excessive copper deposition in WD. Readers interested in symptomatic treatment for liver failure (for instance, drugs to reduce portal hypertension, or intervention for portosystemic varices), or neurological symptoms (for example, dopaminergic drugs and botulinum toxin for various movement disorders; or medication for depression and behavioral problems) are refereed to recent reviews by Pfeiffenberger et al.[9] and Litwin et al.,[10] respectively. The use of liver transplant in patients with WD is also outside the scope of this article and has been reviewed elsewhere.[11–13]

Methods

We searched the PubMed database using variant names of the disease, "Wilson's disease," "Wilson disease," and "hepatolenticular degeneration," in combination with treatment-related terms, "treatment," "BAL," "dimercaprol," "penicillamine," "dimercaptopropane sulphonate," "unithiol," "trientine," "zinc," and "tetrathiomolybdate." We restricted our search to English language articles involving human subjects in which these terms appeared in the title or abstract, and which were published between January 1, 1950, and the date of search. The search was first performed in May 2017 and the results were subsequently updated to be current until October 15, 2017.

The search identified 1,184 candidate articles. We then screened the titles and abstracts of these papers to check if they fell within the scope of this review. At this stage 666 articles were excluded because of lack of relevance (not related to WD; not related to treatment of WD; related to animal studies, unestablished treatments, liver transplant, apheresis, or symptomatic medical or surgical interventions). An additional 74 articles had to be excluded since their abstracts or full texts were not accessible; these tended to be among the older articles in the database and their exclusion is not expected to affect the substance of this review.

The remaining 444 papers were selected for further review. Of these about 70% (315) were case reports or cohort studies. In addition, there were 95 review articles; 30 letters, editorials or commentaries; two guidelines;[14,15] and two systematic reviews.[16,17] Among the 315 patient studies 78% (247 studies) included fewer than 30 participants, and only 6% (18 studies) had 100 or more subjects (notably, 13 of these studies were published within the last decade). Except for one randomized control trial,[18] all the patient studies were cross-sectional or longitudinal observational studies. We also reviewed cross-references of selected publications for added perspective.

Results

The aim of the survey was to address two main questions: what patient population should be treated and what are the available treatment options. Below we summarize our findings and outline the history of development, indication of use, dosing recommendations, efficacy, and adverse effects associated with each drug currently used for definitive medical treatment of WD.

Treatment populations

Copper is an essential micronutrient. The normal diet contains 1–2 mg/day of copper of which 85–95% is excreted into the bile by the liver. Urinary excretion of copper is negligible and there are no insensible losses.[19] It is estimated that because of impaired biliary excretion of copper, patients with WD may gain up to 1 mg of copper per day.[20] The copper accumulation commences at birth but patients usually remain asymptomatic for the first one to two decades of life. Over time, copper-related tissue injury leads to symptoms and signs of liver failure, extrapyramidal syndromes, or behavioral problems. Copper also deposits in the cornea, although it does not impair vision. Eventually, unless treated, continued copper accumulation leads to death from progressive liver failure or from complications of severe neurological disability.[8]

The aim of treatment is to remove the accumulated copper and prevent further copper gain. While justification of treatment in symptomatic patients is obvious, treatment of patients who have not yet developed symptoms is also needed in order to restore normal copper balance and pre-empt symptom onset. In both symptomatic and asymptomatic patients, treatment needs to be continued lifelong to prevent a positive copper balance from dietary copper gain.

Patients heterozygous for ATP7b mutations (one normal and one abnormal ATP7b allele) do not have WD and do not require treatment (Table 1).[14,15,21,22]

Treatment options

Copper is ubiquitous in food and water supplies. A low-copper diet does not prevent copper gain and is unnecessary.[23] During the initial period of copper chelation in symptomatic patients some clinicians suggest avoidance of copper-rich foods such as shellfish, liver, cocoa, nuts, chocolate, mushroom, and dried fruits. These dietary restrictions may be relaxed after a few months.[14,15,23]

Medical treatment options of WD are drugs that chelate copper and those that prevent gastrointestinal copper absorption. In order of introduction, the available copper chelators are dimercaprol, penicillamine, dimercaptopropane sulfonate, and trientine. Zinc administered in the form of zinc salts decreases intestinal dietary copper absorption. Ammonium tetrathiomolybdate (TTM) is a promising newer therapy that both chelates copper and blocks copper absorption in the intestine (Table 2). Interestingly, all these drugs have been developed by individuals or small research groups rather than large multinational pharmaceutical companies.[14,15,24,25]

Table 1. **Treatment Options and Strategies in Wilson Disease**[14,15,25]

Patient Population	Treatment Aim	Treatment Options[1]	Treatment duration
Symptomatic Wilson disease	Initial intensive treatment: Reverse neurological disability and stabilize liver disease; i.e., normalize positive body copper balance	Oral copper chelator (penicillamine or trientine)[2]	Typically takes 1–2 years. Up to 3 years in patients with severe neurological disability
	Maintenance treatment (is commenced once patients have recovered clinically): Prevent positive copper balance	Oral copper chelator (penicillamine or trientine) or zinc[2]	Lifelong
Asymptomatic Wilson disease	Maintenance treatment: Prevent positive copper balance	Oral copper chelator (penicillamine or trientine) or zinc [2]	Lifelong
During pregnancy		Optimize treatment before planned pregnancy Continue oral copper chelator (penicillamine or trientine) (reduce dose by 25%) or zinc Avoid breast-feeding post pregnancy as both the oral copper chelators and zinc salts are secreted in breast milk and may interfere with the infant's copper metabolism	
First-degree family members	Screen for Wilson disease and treat if diagnosis confirmed		Lifelong if Wilson disease diagnosis confirmed No treatment if Wilson disease excluded Continued surveillance for symptoms every 6–12 months if Wilson disease could not be excluded
Wilson disease gene carriers	Do not have Wilson disease and do not require treatment		

[1]Only mainline treatment options are listed here. See text for discussion of dimercaprol (BAL) and tetrathiomolybdate.
[2]Combination therapy of oral chelator and zinc is generally not recommended (see text).

Dimercaprol. Dimercaprol (2,3-dimercapto-1-propanol), or British anti-Lewisite (BAL), was developed in 1940 by Sir Rudolph Albert Peters' group at the University of Oxford, UK, amid great secrecy, as an antidote to an arsenical chemical weapon (lewisite) during World War II.[26] BAL is an alcohol with two substituted sulfhydryl groups (dithiol) that form a stable five-membered ring with trivalent arsenic, and neutralize its toxicity. BAL was chosen over other dithiols as it could be safely applied on human skin and was effective. It is estimated that almost 56 million tubes of BAL ointment were distributed among US troops and there were contingency plans to produce 200,000 pounds of the drug annually, in case arsenic was used as a chemical war agent.[27] Shortly after its introduction as an antidote to arsenic, BAL was shown to increase excretion of other metals such as gold, mercury, silver, and copper. There was also evidence to suggest that BAL promoted excretion of copper in preference to metals such as iron and zinc.[3]

Therefore, once it was demonstrated that WD resulted from excessive copper deposition, John Cumings, at the National Hospital in London, and Derek E. Denny-Brown and Huntington Porter, at the Boston City Hospital and Harvard Medical School in Boston, independently thought of using BAL, and showed that BAL led to copper excretion and clinical benefit in WD.[3–5,28] Denny-Brown and

Table 2. **Medical Therapies for Wilson Disease**

Drug	Mechanism of Action	Route of Administration	Potential Duration of Therapy
British anti-Lewisite or dimercaprol[1]	Copper chelation	Deep intramuscular injection in buttocks	A few weeks or months with drug-free intervals
Penicillamine	Copper chelation	Oral	Lifelong
Trientine	Copper chelation	Oral	Lifelong
Zinc salts	Decreases gastrointestinal copper absorption	Oral	Lifelong
Tetrathiomolybdate[2]	Copper chelation + Decreases gastrointestinal copper absorption	Oral	A few months[2] (see text)

[1]British anti-Lewisite is no longer used in regular practice as it requires painful intramuscular injections and is associated with serious adverse effects and tachyphylaxis. There is suggestion for short-term use of British anti-Lewisite in patients with severe neurological disability (see text).
[2]Under clinical investigation; not commercially available.

Porter also showed dramatic improvement in behavior and movement disorders in five severely incapacitated patients with WD on prolonged use of BAL. This work generated considerable enthusiasm and interest in both the medical fraternity and the popular press, and it is thought to have contributed to the evolution of neurology from a descriptive and palliative discipline to a therapeutic branch of medicine.[3,5,28]

BAL was given as repeated courses of multiple daily injections continued for several weeks at a time. These intramuscular injections were painful and often led to hematomas and sterile abscesses at the injection site.[3,4,23] Adverse effects were observed in around 50% of patients. Dose-dependent hypertension and tachycardia were most frequent. Also seen were anxiety, restlessness, nausea and vomiting, headache, parasthesias, dysesthesias, chest constriction, abdominal pain, flushing, sweating, conjunctivitis, blepharospasm, lacrimation, rhinorrhea, and salivation. Approximately 30% of children developed drug-induced fever.[29,30] As BAL was reconstituted in peanut oil, it was contraindicated in patients with peanut allergies.[27] Besides these issues, the major problem with the use of BAL was development of tachyphylaxis with waning clinical benefits and re-emergence of symptoms. An explanation is that repeated courses of BAL resulted in liver enzyme induction and auto-oxidation of the two sulfhydryl groups of the drug and drug tolerance.[31]

Currently, BAL has almost entirely been replaced in routine clinical use by the two oral copper chelators, penicillamine and trientine. Unlike these two, BAL is lipophilic and has good penetration through the blood–brain barrier. Therefore, some have suggested that BAL might be helpful as a short-term therapy in patients with severe neurological disability.[23,32,7,31,33] Scheinberg and Sternlieb[23,32] (1984, 1995) recommended a 1-month course of BAL in combination with penicillamine. They advise that 1.5 mL (10% suspension in peanut oil) of BAL be given twice a day as deep intramuscular injections in the buttocks (alternating between the right and the left buttock), three to five times a week. The injections should be given in the top lateral quadrant of the buttock with subsequent injections two inches below the previous one. This would allow 10 injections in both buttocks before the need to return to the original injection site after about 2 weeks. If there are no muscular hematomas the course of BAL may be extended to a second month after a drug holiday of 1–2 weeks to prevent tachyphylaxis.[23,32]. In the last few decades BAL use has been reported only in isolated case reports.[34] There have been no recent trials or updates of use of BAL for WD.

Unithiol (dimaval; 2,3-dimercapto-1-propane sulfonate [DMPS]) is a sulfonic acid derivative of BAL that can be administered orally. Other than a few reports of its use,[35–37] there is not enough information available about unithiol to provide any recommendations.

Penicillamine. In 1950, while studying amino acid secretion in liver diseases at the Charles Dent laboratory, University College Hospital, London, John Walshe identified a new sulfur-containing amino acid (dimethyl cysteine) in the urine of a patient who had had a recent liver lobectomy and had received penicillin antibiotic. Later, while working with Charles Davidson at the Thorndike Memorial Laboratory, Boston City Hospital, he saw a patient with WD referred by Denny-Brown for management of liver failure. Based on his prior study, Walshe conceptualized that dimethyl cysteine had the requisite structure to chelate copper. As predicted, the compound led to brisk cupriuresis in the patient. Subsequently, working at the University of Cambridge, Walshe showed that penicillamine was an effective and safe oral copper chelator with dramatic and sustained clinical benefit in patients with WD.[38–40]

Penicillamine (D-penicillamine, $\beta\beta$ dimethyl cysteine, thiovaline) is a thiol with a sulfhydryl group that binds copper and facilities its excretion into urine both in normal people and in patients with Wilson disease.[39,41] The D-isomer, referred to as d-penicillamine, is used clinically (the L-isomer is toxic).[7] Oral penicillamine in doses of 1–2 g per day can initially lead to up to 9 mg of cupriuresis per day in drug naïve patients.[19] The rate of copper excretion with penicillamine is

larger than that with BAL.[20,30,39] While BAL doubled urinary copper excretion in two patients with WD, in the same patients, penicillamine increased urinary copper excretion nine- to 17-fold.[30,41] Penicillamine mobilizes tissue copper stores and long-term use is associated with normalization of body copper balance. As tissue copper stores decrease, penicillamine-induced copper excretion decreases, typically by the end of one year.[19,30,42] As opposed to BAL, penicillamine is not associated with tachyphylaxis.[31]

Penicillamine is recommended for use in symptomatic patients during the initial intensive phase of treatment and later as maintenance therapy. It is also recommended in presymptomatic patients.[14–16,22] The therapeutic response is best seen clinically. The liver dysfunction usually stabilizes and histological improvement has been demonstrated. Neurological disability reverses in a majority of patients.[23,31,43,44] There is improvement in movement disorders as well as in cognitive and behavioral problems. Patients with severe cognitive and physical disability can also recover and resume normal lives. Kayser–Fleischer rings decrease and resolve. This clinical recovery is associated with reduction of brain magnetic resonance imaging (MRI) abnormalities.[23,31,43,45]

In most patients penicillamine can be safely administered long term, with close monitoring for adverse effects and medication compliance. S.F., the first patient ever to receive penicillamine, recovered from severe neurological disability and returned to normal life. As per the last report, she had been on penicillamine for 47 years, raised three children and continued to be normal.[38] Similar good outcomes have been shown in recent longitudinal studies involving large patient populations.[43,44,46,47] Penicillamine can be given during pregnancy. In fact, discontinuation of penicillamine during pregnancy has led to deterioration of WD. Breast-feeding however should be avoided as penicillamine is excreted in breast milk and may interfere with the infant's copper metabolism.[14,15,23,48]

In symptomatic adults, penicillamine is given in doses up to 1.5–2 g per day. The dose may be reduced to 500–750 mg per day once patients have recovered clinically, thus indicating that normal copper balance has been achieved. The maintenance therapy needs to be continued lifelong to prevent re-accumulation of dietary copper in the body. The dose in children is 20 mg/kg/day (rounded to the nearest 250 mg).[21] Food reduces penicillamine absorption by over 50%; therefore the drug should be given on an empty stomach (fasting is advised; preferably fasting 3–4 hours before and 2–4 hours after the drug is taken). Separating drug doses from meal times is difficult and feasible with, at most, twice a day dosing (typically early morning and midway between lunch and dinner).[14,15,21,25] Penicillamine has been shown to have an antipyridoxine effect. Most clinicians therefore supplement pyridoxine (vitamin B6) in all patients on penicillamine though some recommend B6 supplementation only in pregnant women, and in cases of acute illness or nutritional deficiencies.[49,50]

Worsening of neurological symptoms soon after starting penicillamine is perhaps the most worrying adverse effect of the drug. The fear of such a worsening often leads to preemptive under-treatment of patients. Neurological worsening is reported in around 10% of patients, though much higher prevalence has also been described.[23,43,51–54] Neurological worsening has also been reported with other treatments for WD including trientine, zinc, ammonium TTM and liver transplant. Some recent studies suggest that the frequency may be similar for penicillamine, trientine, and zinc and less than 10%.[46,47,52] The mechanism of neurological worsening is unclear and it is not yet possible to predict which patients may worsen with copper chelation. One hypothesis is that treatment leads to sudden mobilization of copper from liver into the blood and then the brain. This released copper may then lead to free-radical induced tissue injury.[53,55] (To mitigate the proposed free radical surge Walshe[31] recommends the addition of oral alpha tocopherol [vitamin E] as a free radical scavenger during the first 3 months of treatment.) In a recent study, the severity of baseline neurologic disability, concomitant use of antidopaminergic agents, and MRI lesions in the brainstem and thalamus were associated with increased risk of neurological worsening.[52] In a majority of patients with drug-induced neurological worsening symptoms remit with brief down-titration of penicillamine. In others, penicillamine should be discontinued and replaced by alternative treatment. In rare instances (1–3% or less) the disability is not reversible.[14,15,23,43] Death from fatal status dystonicus that developed a few weeks after initiation of penicillamine has been reported.[56] Urgent liver transplant as rescue treatment for neurological deterioration has shown variable results.[24] A pragmatic approach to prevent neurological deterioration is to start penicillamine in low doses and slowly escalate the doses every few weeks with careful clinical monitoring. In case of clinical deterioration the doses can be promptly reduced and then slowly up-titrated on clinical recovery.[14,15,25,57]

Penicillamine is also associated with some early-onset and late-onset adverse effects. The early reactions are seen in 10–20% patients, typically within the first few weeks of drug use, and include fever, skin rash, lymphadenopathy, and cytopenias. These are dose-dependent hypersensitivity reactions to penicillamine that abate with down-titration of the doses, or with a brief course of oral steroids.[23,46,58] Early-onset penicillamine induced pancytopenia is rare and necessitates drug withdrawal. In contrast to these early-onset adverse effects, late reactions are infrequent and are observed after years and decades of penicillamine use. Though uncommon, late-onset hypersensitivity reactions are potentially fatal. They include drug-induced lupus or isolated nephrotic syndrome, leading to transient or progressive renal failure and in some cases end-stage renal disease. Rare instances of Goodpasteur's nephritis, optic neuropathy, arthropathy, or drug-induced myasthenia have been reported. In case of mild reactions, down-titration, or temporary drug cessation may be attempted in addition to symptomatic treatment. However, in case of severe reaction it may be prudent to withdraw penicillamine immediately and substitute with trientine.[59–66] In a small subset of patients though, similar hypersensitivity-related reactions also develop with the use of trientine. In a study, elevated serum antinuclear antibodies did not help predict long-term penicillamine associated immunological reactions.[67] Overall, most of the penicillamine-induced immunological adverse effects can be managed by concomitant steroids.[43,46] On prolonged penicillamine use, patients may also develop various skin lesions related to interference of penicillamine with collagen and elastin linking. These are

rare idiosyncratic reactions and include penicillamine dermatopathy and elastosis perforans serpiginosa. They are usually of cosmetic concern alone and treated symptomatically. Easy bruising and subcutaneous nodules are rare with maintenance doses of less than one gram per day. Penicillamine related pemphigus lichen planus and painful stomatitis have also been described.[68–75]

Trientine. The need for an alternative to penicillamine arose with reports of penicillamine-induced nephropathy and renal failure in some patients with WD. Penicillamine had to be discontinued in these cases, which led to worsening of WD. Other existing treatments, including BAL and zinc, were not well tolerated and there was fear that the patients could die from WD without copper chelation.[76] Hall Dixon,[77] from the Department of Biochemistry at the University of Cambridge, suggested use of triethylene tetramine, an industrial chemical used for hardening epoxyresin. This is an amine with structure similar to the naturally occurring amines, spermidine and spermine, and therefore was presumed safe for use in humans. However, triethylene tetramine is very alkaline with pH 14 and the commercially available industrial formulation had around 40% impurities including triaminotriethylamine that is possibly associated with acute tubular necrosis. Dixon neutralized the amine with hydrochloric acid to generate crystalline salt, trientine dihydrochloride (triethylene tetramine; *N,N′*-bis(2-aminoethyl)-1,2-ethanediamine, trien).[7,77] Trientine dihydrochloride, commonly referred to as simply trientine, is very hygroscopic and requires airtight storage.[7]

The four amino groups of trientine form a stable ring complex with copper, and facilitate cupriuresis. In contrast to BAL and penicillamine, trientine does not have sulfhydryl groups. Trientine was used in patients after safety was demonstrated in rats.[7] Based on clinical and radiolabeled copper studies Walshe[78] showed that trientine led to brisk urinary copper excretion (at a rate similar to penicillamine) in patients who are drug naïve, or those who had received only short-term penicillamine treatment and therefore had a large positive copper balance. In contrast, in patients who had been on long-term penicillamine treatment and therefore did not have a significant positive copper balance, trientine led to a lesser degree of cupriuresis than penicillamine. He thus hypothesized that the two drugs chelated copper from different stores in the body (a store of labile copper and a store of copper that is "more firmly attached to tissue proteins").[78]

Trientine was developed as, and has proved to be, a life-saving treatment option in patients in whom penicillamine had to be discontinued due to adverse events.[79–81] Subsequently, trientine has been used successfully in patients with decompensated liver failure.[82] It is now also used as a first-line therapy in the initial intensive and the later maintenance phase of treatment in symptomatic patients. Trientine is also recommended in asymptomatic patients with WD. It can be continued safely as a long-term therapy.[46,76,78,81,83–91] Trientine can be given to pregnant women. It is recommended that breast-feeding be avoided during trientine treatment (Table 2).[14,15,92]

As with penicillamine, trientine doses have to be taken at a different time from meal times. Recommended doses for initial intensive chelation in adult symptomatic patients are 900 mg to 2 g, given in two to three divided doses. The dose may be reduced to 600–900 mg per day for maintenance therapy in symptomatic patients, and a similar dose may be used in adult asymptomatic patients.[15,93] In children, the recommended dose of trientine is 20 mg/kg/day (rounded to the nearest 300 mg).[21] It has been suggested that once-daily trientine dosing might be sufficient as a maintenance therapy.[94,95] If confirmed in larger studies, such a dosing schedule would help improve patient compliance with treatment

Trientine, as is true for penicillamine, can lead to neurological deterioration. In recent studies, the risk of neurological deterioration with trientine is similar to that with penicillamine.[46,52] The symptoms usually resolve with a reduction of the drug dose.[46,86,96] Early-onset hypersensitivity reactions are less frequent with trientine than with penicillamine. Among the late-onset hypersensitive reactions, both drug-induced lupus and nephritis (as with penicillamine) have been observed with trientine. Management involves dose reduction and use of steroids. In cases of severe reaction, it is best to substitute trientine with an alternative treatment.[23,25,54,91] Trientine can form toxic complexes with iron and the two should not be given concomitantly.[15] There are isolated reports of trientine-induced sideroblastic anemia that reversed with a reduction in trientine doses.[97] Pancolitis, requiring trientine withdrawal, has also been described.[98] Skin rash, loss of taste, and hemorrhagic gastritis have been reported in patients with primary biliary cirrhosis receiving trientine.[99] There is a report of a patient developing dizziness and vomiting 24 hours after ingestion of 6 g of trientine with suicidal intent. The symptoms remitted within 48 hours.[100]

Tetrathiomolybdate. Molybdenum is an essential micronutrient present in food. It has long been known in veterinary medicine literature that in Australia sheep grazing on sulfur-rich and molybdenum-contaminated pastures developed copper deficiency syndrome (known as 'teart disease'). These reports suggested use of molybdates for treatment of WD in the 1940s once it was recognized that WD resulted from copper toxicosis. However, an early study of molybdenum failed to show clinical or biochemical benefit in patients.[101] An explanation is that unlike the ovine abomasum (fourth stomach), the human gastric mucosa does not reduce molybdate to TTM. And, unlike TTM, molybdate does not have anti-copper properties. In the 1980s when Walshe and Stuart Laurie, an inorganic biochemist from University of Leicester, were searching for an alternative treatment of WD, they considered using a reduced form of molybdate, ammonium TTM, for treatment. To check for possible adverse effects Walshe[7] took the drug himself for a week and having suffered no ill effects, prescribed it to his patient. This patient who was intolerant to penicillamine, trientine, and BAL, improved neurologically with 30 mg twice a day dose of ammonium TTM. And at the end of 1 year of treatment with the drug, his liver histology had normalized.[102]

Radiocopper studies showed that ammonium TTM (commonly simply referred to as tetrathiomolybdate or TTM) given orally almost completely blocks dietary copper absorption by forming complexes with copper and proteins in the gut lumen. These complexes are not absorbed by the intestinal cells and are eliminated in the feces. TTM is

more effective than zinc in preventing dietary copper absorption and, unlike zinc, its action is immediate. Besides preventing copper absorption, both parenteral and oral TTM chelates tissue copper by forming inert complexes with copper and proteins.[102] Oncology studies suggest that TTM may decrease angiogenesis, fibrosis, and inflammation by inhibiting various copper-dependent cytokines.[103,104]

A number of dosing regimens have been tried for TTM, all of which require multiple doses of the drug per day. For instance, six daily doses have been used, three with meals to prevent dietary copper absorption and three in-between meals to chelate tissue copper.[18,102,105–110] Though there is a report of its use for 8 years,[111] present recommendations are that treatment with TTM be limited to a few months.[104]

The safety and efficacy of TTM have been studied for use as initial therapy in patients with neurological symptoms.[105–109] It has also been compared with trientine in such patients.[18,110] Adverse effects have been infrequent and included reversible bone marrow depression, rise in aminotransferases, acute hepatitis, markedly elevated triglycerides and cholesterol levels, and seizures.[106,112,113] TTM-induced copper deficiency-related cytopenias have also been reported.[114] There is concern about the safety of TTM use in children and adolescents as TTM has been shown to impair epiphyseal bone growth in animal studies.[111] Drug-induced neurological worsening has been reported but is possibly less common than that reported with trientine or penicillamine.[18,106,111]

In the last 35 years TTM has been used as an experimental drug in closely monitored research settings.[7] Both ammonium TTM, and the more recently developed choline TTM, are promising therapies for WD that are under phase 2 and phase 3 multinational clinical trials. They are not as yet commercially distributed.[104]

Zinc. Gerrit Schouwink, a Dutch neurologist, in his MD thesis[7] for the University of Amsterdam in 1961, showed that zinc (in the form of zinc salts) could reduce intestinal absorption of copper and be used for treatment of WD. Later, zinc therapy was supported and popularized by Tjaard Hoogenraad and George Brewer.[31,115–117]

Zinc given orally (as zinc salts) is absorbed by the intestinal cells and increases production of metallothionein in the cells 25-fold within 2–3 weeks of initiation of therapy. Metallothioneins are cysteine-rich proteins that can bind various metal ions and are normally present in the intestine, liver, brain, and other tissues. They have a stronger affinity for copper than for zinc. The zinc-induced metallothionein in enterocytes thus preferentially binds to dietary copper and copper secreted into the gut. The copper bound to metallothionein is sequestered within the intestinal cells and prevented from absorption into the blood. The metal is subsequently lost in feces when the enterocytes are shed in the intestinal lumen during normal cellular turnover. Therefore, zinc may cause a slow negative copper balance. Zinc may also stimulate metallothionein production in the liver.[15,118]

Zinc is recommended as maintenance therapy in symptomatic patients once symptoms have regressed following treatment with oral copper chelators.[15] It has also been given as the first-line therapy in asymptomatic patients.[119,120,121] However, there are reports of deterioration in liver function in asymptomatic patients while on zinc therapy.[122–124] Though zinc is well tolerated by children with WD,[125–127] some investigators have raised concerns about the long-term consequences of use of zinc in children because (unlike oral copper chelators) zinc may not reduce liver copper content and it has the potential to induce copper deficiency.[14,15]

Zinc has also been used at some centers as treatment in patients with symptomatic liver disease[116,117,128–131] and symptomatic neurological disease.[47,132–135] Some studies indicate that patients with liver disease may be less responsive to zinc than patients with neurological impairment.[130,136] Both hepatic and neurological deterioration have been reported in some symptomatic patients receiving zinc.[31,33,47,130,137] Currently, the use of zinc in symptomatic patients is not widely accepted.[138]

Zinc is administered as sulfate, acetate, or gluconate salts. These are given as 150 mg of elemental zinc in adults, or as 75 mg in children, in two to three divided doses per day.[21,120,139] As with penicillamine and trientine, food interferes with absorption of zinc and therefore zinc should not be given at meal times. Zinc-induced gastric irritation is common and limits zinc doses. It is the most common reason for discontinuation of the drug by patients. Drug tolerance can be improved by switching to an alternative zinc salt; generally, acetate and gluconate salts are better tolerated than sulfates. Another strategy is to give the drug in the mid-morning rather than before breakfast. Addition of a small protein meal may further mitigate the gastric symptoms.[21,140] Zinc can be safely continued during pregnancy.[141]

Except for gastric symptoms, zinc has few adverse effects. Zinc can lead to neurological deterioration after commencement of therapy. The incidence of such deterioration has been reported to be similar to that observed with penicillamine and trientine.[47,136] The mechanism of zinc-induced neurological deterioration is unclear and is probably different from that associated with oral chelators. Zinc can also lead to anemia, and isolated increases in lipase and amylase have been described.[33,142] There are isolated reports of copper deficiency-related anemia, neutropenia, sensorimotor neuropathy, or myelopathy that developed following long-term use of zinc (for treatment of WD or other illnesses, or as an over-the-counter health supplement). The myelopathy is characterized by demyelination of dorsal spinal columns, and is similar to that seen with vitamin B12 deficiency. The biochemical and clinical features of zinc-induced copper deficiency generally improve with copper replacement (foods rich in copper) and reduction in zinc doses,[143–145] although there are reports of persistent symptoms despite copper correction.[146,147] (As noted earlier, copper deficiency has also been described in association with TTM,[114] although, to our knowledge, cases of copper deficiency following treatment with penicillamine or trientine have not been reported.)

Zinc and oral chelators (penicillamine and trientine) have different mechanisms of action, which suggests that there may be potential benefit of using them in combination. On the other hand, there are pragmatic problems in scheduling the drug doses for such a combination therapy. If given together, the oral copper chelators chelate zinc and that decreases the bioavailability and efficacy of zinc and

those of the chelators.[148] Thus the oral chelator and zinc have to be given in multiple daily doses, separated both from meal times and from each other, which is practically difficult and reduces compliance.[149]

A few individual studies have found a combination therapy using zinc and an oral chelator to be beneficial. However, a systematic review of such combination therapies found that overall they have a lower rate of effectiveness, a higher rate of adverse effects, and higher mortality than monotherapies (oral chelator or zinc alone).[17] For example, there is potential risk of severe sideroblastic anemia following use of zinc with trientine.[150] For these reasons the use of combination therapies is generally not recommended.

Discussion

From the time of introduction of penicillamine, WD has been a treatable disorder. Patients with WD can be expected to live healthy and normal lives. If WD is diagnosed in the presymptomatic stage, symptom onset and copper-related tissue injury can be prevented.[14,15] If WD-related neurological disability has already developed at diagnosis, this too can be reversed in most patients.[23,31,43,44,54] WD-related liver failure can also be stabilized.[23,31,43,45]

The mainstays of treatment of WD are the two oral chelators, penicillamine and trientine. Recent, relatively large, patient studies from various parts of the world have confirmed earlier reports that both penicillamine and trientine are generally safe and effective. They also suggest that there is no major difference in the expected clinical benefits or adverse-effect profile for the two drugs, although no direct comparative studies have been conducted. At present, therefore, the choice of drug is governed mainly by their availability and personal experience in their use. The cost of the drug may also play a role; for instance, in India trientine has to be imported and is a thousand times more expensive than penicillamine, which is manufactured locally. Zinc is another treatment option during the maintenance phase of treatment, and TTM is a promising alternative currently being studied.

However, all currently available WD treatments are associated with adverse effects (such as neurological worsening) in a subset of patients, which can require adjustment, substitution, or even discontinuation of treatment. These adverse effects also reduce the patient's compliance with treatment, which by itself can lead to clinical deterioration and even death.[6,57,151–153] An approach to deal with this issue is to systematically monitor the patient under treatment so that treatment effectiveness, adverse effects, and treatment non-compliance are tracked and the treatment adjusted accordingly. In recent years, two WD-specific clinical scales, the Unified Wilson Disease Rating Scale (UWDRS) and the Global Assessment Scale for Wilson Disease (GAS for WD), have been introduced for this purpose.[154–156]

Another complementary approach is to pre-emptively identify the subset of patients that can be expected to experience adverse effects. Clinical studies to identify markers for such patients are at a preliminary stage. These efforts have benefited from the improvement in study design and increase in study size that has been seen in recent years. Growth of WD referral centers and international multicenter collaborative projects has made such large studies increasingly feasible.

Besides clinical, imaging, and biochemical markers, genotyping is also a potential tool for selecting treatment for WD patients. Recent mapping studies have shown that the *ATP7B* mutation shows geographical variance.[157,158] And genotype–phenotype analysis in cell models indicates that certain mutations are associated with more severe phenotypes than seen with other mutations.[158] This mutation-specific variance has been reported at the cellular level to correlate with the degree of loss of ATP7b protein function.[159,160] In the future, such research developments can be expected to move to the clinical stage and allow one to predict the likely disease course and drug response in individual patients, and thus tailor treatment.

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