An Update on the Future of Wilson Disease Management

Robert S. Brown, Jr, MD, MPH

Wilson disease (WD) is a rare autosomal recessive genetic disorder of copper metabolism. Although WD was first described as progressive lenticular degeneration in 1912,[1] and established as a condition related to elevated copper levels in 1948,[2] it was not until 1956 that the copper chelator penicillamine was introduced[3] and 1993 that mutations in the *ATP7B* gene were implicated as the causative underlying genetic abnormality.[4] With a broad range of symptoms, including dysarthria, dystonia, tremor, chorea, athetosis, and, in later stages of disease, hepatic failure and neurologic disability, the differential diagnosis of WD may be challenging, leading to delays in initiation of effective therapy.[5] Although heterozygous mutations of *ATP7B* may be present in up to 2.5% of the population,[6] clinical disease manifests in approximately 1 in 30,000 to 100,000 individuals.[7] WD usually presents in childhood into early adulthood; however, a wider range of ages at onset is recognized.[8] While it is extremely rare for WD to present after the age of 35, late-onset cases are reported. Given the myriad manifestations of WD, its rarity, and its diversity of presentations, diagnostic acumen and a knowledge of the latest updates in the field, as well as novel therapies in late-stage development, are crucial in ensuring appropriate management.

From a pathophysiologic perspective, WD is caused by dysregulation of the tightly regulated system of transport, retention, and excretion of copper from the diet. Of the roughly 2 to 5 mg of dietary copper ingested daily by an average individual, approximately 2% is retained in the body for use in enzymatic activity, and the remaining portion is excreted in bile.[9] This process involves multiple transporters. Copper is first absorbed within the small intestines through nonspecific metal uptake transporters, exported from the small intestine to the portal circulation via P-type ATPase copper transporters, and absorbed from portal circulation to the liver via the CTR1 transporter. Within the liver, the ATP7B transporter regulates incorporation of copper into the carrier protein ceruloplasmin, as well as excretion of copper through the biliary system.[9] In patients with *ATP7B* mutations, this crucial transport function is impaired, resulting in deficient levels of ceruloplasmin and an accumulation of unbound copper within the liver that ultimately reaches other vital organs, including the brain, eyes, and kidney, resulting in clinical signs and symptoms.[10]

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Robert S. Brown, Jr, MD, MPH, is affiliated with Weill Cornell Medicine, New York, New York.

CME Objective

After completing this educational activity, you should be able to:

- Implement an individualized treatment strategy for the patient with Wilson disease, while watching for new options that could resolve unmet needs

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Review Process
The author agreed to provide a balanced and evidence-based presentation and discussed the topic and CME objective during the planning sessions. The author's submitted content was validated by CME Institute staff, and the activity was evaluated for accuracy, use of evidence, and fair balance by a peer reviewer who is without conflict of interest.

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Case Practice Question

Discussion of best response can be found at the end of the activity.

Charles is a 12-year-old male with suspected Wilson disease presenting with ataxia and other neurologic symptoms. Which of the following features would be suggestive of Wilson disease in this patient?

a. Elevated levels of ceruloplasmin
b. The patient cannot have Wilson disease, as cases usually present after age 40
c. Mutations in the *ATP7B* gene
d. Wilson disease can be ruled out due to the lack of liver disease

The management of WD has evolved over the years. Current guidelines[10] for diagnosis and treatment of WD in adults published by the American Association for the Study of Liver Diseases in 2008 and pediatric guidance[11] published in 2018 recommend use of chelation therapies to decrease total body copper stores as well as zinc to reduce intestinal copper absorption. While penicillamine therapy remains a standard treatment for WD,[11] trientine is becoming a preferred first-line treatment for WD due to lower rates of side effects and superior tolerability compared with penicillamine.[12] Another chelating agent, tetrathiomolybdate (TTM), was not widely available at the time of publication due to chemical instability of the ammonium salt used initially for WD treatment[12] but is mentioned in guidelines[10] as an experimental decoppering therapy in the United States and Canada. However, a more stable form of this potent and multimodal decoppering agent, bis-choline TTM, has been developed and promising results were reported in a phase 2 clinical trial.[13] A phase 3 clinical study[14] is underway in patients with WD with a 48-week double-blind phase and an extension period of up to 60 months.

Table 1. Common Therapies Used in the Treatment of Wilson Disease[a]

Therapy	Year of introduction	Mechanism of action	Summary of efficacy and adverse events leading to treatment discontinuation
Penicillamine	1956	Copper chelation	• Promotes copper urinary excretion of 200-500 µg per 24-hour period in the maintenance phase, with excretion rates exceeding 1000 µg per 24-hour period in the initial phase • AEs are reported in 20% to 30% of patients during treatment and include "early" AEs (eg, fever, cutaneous manifestations, arthralgia) and "late" manifestations (eg, paradoxical neurological worsening, renal insufficiency, lupus-like syndrome)
Zinc salts	1961	Decreased GI absorption of copper	• Copper urinary excretion < 75 µg per 24-hour period, with NCC levels ranging from 5-15 µg/dL (> 12 months of treatment) • AEs reported in 3% to 7% of patients, with the most common being gastritis, biochemical pancreatitis, immunosuppression, and bone marrow depression
Trientine	1982	Copper chelation	• Promotes copper urinary excretion of 200-500 µg per 24-hour period in the maintenance phase, with excretion rates exceeding 1000 µg per 24-hour period in the initial phase • AEs in 7.1% of patients, with the most common being gastritis, sideroblastic anemia, lupus-like reactions, and loss of taste
Bis-choline tetrathiomolybdate	In phase 3 evaluation as of 2022	Copper chelation and decreased GI absorption of copper	• On a primary endpoint of change in baseline NCC concentration at 24 weeks and with maintenance of normalized NCC levels of 2.3 µmol/L or lower, or at least a 25% reduction from baseline, 71% of patients met criteria for treatment success. Mean NCC levels were reduced by 72% from baseline to week 24 ($P < .0001$) • AEs were reported (psychiatric disorders, gait disturbance, elevated liver aminotransferases, and decline in neurological functioning), although only 4 of 11 AEs observed were considered possibly or probably related to study medication

Abbreviations: AE = adverse event, GI = gastrointestinal, NCC = non-ceruloplasmin-bound copper.
[a]Based on Członkowska et al[6] and Weiss et al.[13]

In a systematic review and meta-analysis[15] rating the comparative effectiveness and safety of common WD therapies, although D-penicillamine was associated with lower mortality versus no treatment, the drug was not associated with a lower risk of mortality and improved rates of prevention or amelioration of clinical symptoms compared with zinc alone. In a 10-year follow-up study of 22 children with WD, treatment with zinc sulfate adjusted by age and weight, starting in presymptomatic pediatric patients, resulted in 73% of children (16/22) having normal alanine aminotransferase levels, concurrent with increased urinary copper excretion.[16] A randomized controlled trial comparing trientine hydrochloride plus zinc with TTM plus zinc in primarily newly diagnosed patients with Wilson disease with neurologic symptoms identified a higher risk of neurologic deterioration in patients receiving trientine versus TTM (6 of 23 patients [26%] vs 1 of 25 patients [4%], $P < .05$).[17] Treatment with another form of trientine—trientine tetrahydrochloride—has also been trialed, with noninferiority to D-penicillamine over 24 weeks of follow-up established in terms of reductions in non-ceruloplasmin copper levels.[18] Clinical efficacy and safety of current therapies and the latest data on bis-choline TTM are reviewed in Table 1.[6,13]

In the modern management of WD, consideration of the latest evidence in both diagnosis and long-term treatment are important in optimizing clinical management. In 2022, clinicians should be aware of the role of copper and mutations of the *ATP7B* gene in disease pathophysiology, as well as the clinical manifestations that may raise clinical suspicion of this rare disease. Through an awareness of key clinical data and novel therapies in late-stage development, clinicians can screen for and maintain awareness of the latest multimodal mechanisms for the management of WD.

Discussion of Case Practice Question

Preferred response: **c. Mutations in the *ATP7B* gene**

Wilson disease symptoms include dysarthria, dystonia, tremor, chorea, athetosis, and ataxia and usually presents in childhood into early adulthood. Heterozygous mutations of *ATP7B* gene are implicated as the causative underlying genetic abnormality, causing impairment in ATP7B transport function which regulates incorporation of copper into the carrier protein ceruloplasmin as well as excretion of copper through the biliary system. This results in deficient levels of ceruloplasmin and an accumulation of unbound copper within the liver that ultimately reaches other vital organs.

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1. **Charles is referred for therapy with trientine plus zinc salts but does not experience regression of neurologic symptoms following 8 weeks of treatment. Which of the following therapies might be an alternative in clinical trials?**
   a. Bis-choline tetrathiomolybdate
   b. Tetrathiomolybdate
   c. Addition of D-penicillamine
   d. British anti-Lewisite

2. **Which of the following treatments for Wilson disease uses both copper chelation and decreased GI absorption of copper as mechanisms of action and has resulted in a decrease in non-ceruloplasmin-bound copper concentration by 72% from baseline over the course of 2 years?**
   a. Trientine tetrahydrochloride
   b. Zinc sulfate
   c. Tetrathiomolybdate
   d. Bis-choline tetrathiomolybdate

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