



Wilson Disease Agents

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OVERVIEW

Wilson disease is an inherited abnormality of copper metabolism that leads to excess copper accumulation and injury to liver, brain and other organs. The metabolic defect in Wilson disease is caused by mutations in ATPase7B, a hepatic enzyme responsible for transmembrane transport and excretion of copper into the bile. The metabolic defect leads to accumulation of free copper in liver and blood and secondarily in other organs, particularly brain and kidney. The disease usually presents in childhood or adolescence with neurologic syndromes, signs of advanced liver disease and hemolytic anemia. If untreated it is invariably fatal, death being from progressive neurologic disease or acute or chronic liver failure. Therapy of Wilson disease is usually based upon copper chelation, but limitation of copper in the diet and approaches to inhibiting copper absorption can also be important.

Copper chelating agents available in the United States include penicillamine, trientine and dimercaprol. These agents lower blood and tissue copper levels and, when given chronically, prevent copper accumulation and injury in Wilson disease. Penicillamine is considered the first line therapy of Wilson disease, but is often limited by its unique side effects that can be severe and may be dose limiting. Trientine is a second line agent and is less effective than penicillamine in chelating copper, but it has fewer serious side effects and is generally well tolerated. Both of these agents are given orally. Dimercaprol (also known as British anti-Lewisite or BAL) was the initial copper chelating agent developed for Wilson disease, but it requires parenteral administration and has frequent serious adverse effects. Dimercaprol is currently rarely used for Wilson disease and generally only in conjunction with oral copper chelating agents, for a short period of time, and in patients with severe symptomatic disease. Zinc is also useful in managing Wilson disease and acts by inhibition of copper absorption, rather than chelation of excess copper in tissue or the circulation. Zinc has been used as a first line therapy, but is currently recommended largely as maintenance therapy once chelation of excess copper has been accomplished.

Among the drugs used for Wilson disease, only penicillamine has been linked to cases of clinically apparent liver injury. Penicillamine has been linked to cases of acute, immunoallergic hepatitis which is likely due to hypersensitivity.

Information on the mechanism of action, clinical use and potential hepatotoxicity of the agents used to treat Wilson disease are given in the individual drug records for each of the following:

- [Dimercaprol](#)
- [Penicillamine](#)
- [Trientine](#)
- [Zinc](#)

ANNOTATED BIBLIOGRAPHY

References updated: 29 September 2014

Byrns MC, Penning TM. Treatment of metal exposure. Environmental toxicology: carcinogens and heavy metals. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1872-6.

(Textbook of pharmacology and therapeutics).

Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. Am J Med 1956; 21: 487-95. PubMed PMID: 13362281.

(Initial studies on efficacy of oral penicillamine [β,β-dimethyl cysteine, a monothiol] in inducing cupruresis in Wilson disease and lack of effect of cysteine and methionine; no toxic reactions were observed).

Sternlieb I, Scheinberg IH. Prevention of Wilson's disease in asymptomatic patients. N Engl J Med 1968; 278: 352-9. PubMed PMID: 5635646.

(Among 42 asymptomatic persons who were diagnosed with Wilson disease and treated with penicillamine for up to 8 years, none developed symptomatic disease).

Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. Lancet 1982; 1: 643-7. PubMed PMID: 6121964.

(Among 20 patients with Wilson disease who were intolerant of penicillamine therapy, all responded to trientine therapy, although complications of penicillamine [lupus syndrome, elastosis perforans] did not always improve; no evidence of toxicity including hepatotoxicity).

Hoogenraad TU, Van den Hamer CJ. 3 years of continuous oral zinc therapy in 4 patients with Wilson's disease. Acta Neurol Scand 1983; 67: 356-64. PubMed PMID: 6613522.

(4 patients [17-46 year old men] with Wilson disease previously treated with penicillamine were treated with oral zinc for at least 3 years and all showed clinical improvement and no adverse events, including no changes in liver tests during zinc therapy).

Brewer GJ, Hill GM, Prasad AS, Cossick ZT, Rabbani P. Oral zinc therapy for Wilson's disease. Ann Intern Med 1983; 99: 314-20. PubMed PMID: 6614680.

(5 patients [25-34 years old, 3 men, 2 women] with stable Wilson disease after penicillamine therapy underwent careful copper balance studies while on zinc therapy alone, demonstrating a negative copper balance largely due to increased fecal loss).

Brewer GJ, Dick RD, Johnson VD, Brunberg JA, Kluin KJ, Fink JK. Treatment of Wilson's disease with zinc: XV long-term follow-up studies. J Lab Clin Med 1998; 132: 264-78. PubMed PMID: 9794697.

(Description of patterns of change in urinary, hepatic and serum copper and zinc levels and liver tests in 141 patients with Wilson disease treated with zinc; adverse reactions were "minimal", the most common being initial abdominal discomfort).

Vilensky JA, Redman K. British anti-Lewisite (dimercaprol): an amazing history. Ann Emerg Med 2003; 41: 378-83. PubMed PMID: 12605205.

(History of development and use of dimercaprol, initially synthesized at Oxford during WWII as a means of reversing Lewisite arsenical gas poisoning [thus British anti-Lewisite (BAL)] and now still used for emergency therapy of heavy metal poisoning: arsenic, gold, copper and mercury).

Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. *Lancet* 2007; 369 (9559): 397-408.
PubMed PMID: 17276780.

(Review of the clinical features, pathogenesis, genetics, diagnosis and treatment).

Roberts EA, Schilsky ML, AASLD. Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008; 47: 2089-111. PubMed PMID: 18506894.

(Thorough review of the cause, natural history, diagnosis and treatment of Wilson disease with specific recommendations for use of penicillamine, trientine and zinc).

Walshe JM. The conquest of Wilson's disease. *Brain* 2009; 132 (Pt 8): 2289-95. PubMed PMID: 19596747.

(History of the initial description of Wilson disease, its link to copper accumulation, and therapies several of which were developed by the author).

Weiss KH, Stremmel W. Evolving perspectives in Wilson disease diagnosis: treatment and monitoring. *Curr Gastroenterol Rep* 2012; 14: 1-7. PubMed PMID: 22083169.

(Review of the diagnosis and management of Wilson disease, including the role of genetic testing and the choice of medical therapies).