Urinary copper excretion upon initiation of treatment is often >1000 μg/24 h and decreases over time on treatment to approximately 3–10 times the upper limit of normal for urinary copper excretion (typically approximately 150–500 μg/24 h).[297]

Generally, with nonadherence to therapy over time, urinary copper rises. In the context of chronic dosing, urinary copper excretion higher than treatment goal may reflect nonadherence, but it can also be due to other causes of insufficient drug action (poor drug absorption, unintentionally low dosing) or intercurrent ALI. Values of urinary copper excretion <100 μg/24 h may indicate some degree of copper deficiency due to overtreatment resulting in excess copper removal. In such a situation, serum copper is expected to be lower than pretreatment values. Reversible sideroblastic anemia and neutropenia may be present. Overtreatment can result in hepatic iron overload in patients with WD, similar to that observed for D-penicillamine.[283] In contrast, when low urinary copper excretion accompanies nonadherence, serum copper increases, reflecting increased NCC.

Zinc (zinc salts)

Zinc was first used to treat WD by Schouwink in the Netherlands in the early 1960s.[298,299] Its mechanism of action differs from that of D-penicillamine and trientine. Zinc inhibits the intestinal uptake of copper by inducing enterocyte metallothionein, an endogenous chelator with a greater affinity for copper than for zinc. Ingested copper taken up into the enterocytes binds to cytoplasmic metallothionein more avidly than zinc. The copper-metallothionein is excreted in the feces as enterocytes are shed in normal turnover.[300] Thus, the copper is not absorbed into the portal circulation. Because copper also enters the gastrointestinal tract from saliva and gastric secretions, zinc treatment generates a negative balance for copper and removes tissue copper, albeit relatively slowly.[301] Zinc may also improve hepatic resistance to copper toxicity by inducing hepatocellular metallothionein.[302] Zinc may reverse Cu-mediated interference with nuclear receptors and thus improve hepatocellular metabolism.[303]

Zinc has very few side effects. Gastric irritation or gastritis is the most common adverse effect, occurring in approximately one third of patients. It may be dependent on the type of zinc salt. In one survey, approximately 38% of patients changed the zinc salt used to treat their WD due to gastrointestinal symptoms.[304] Gastric irritation rarely is severe. In children, zinc sulfate may be problematic: in one pediatric case, gastric perforation occurred.[305,306] Changing to a different salt or taking zinc with a very small amount of protein may alleviate symptoms. Zinc treatment to block dietary copper absorption is effective in the majority of but not all patients with WD. In the initial studies by Brewer et al., some individuals failed to have adequate blockage of dietary copper.[307] Hepatic deterioration was occasionally reported in WD on zinc monotherapy and was fatal in one case[308–310]; however, it is unknown if these individuals were properly adherent to their therapy. Early paradoxical neurological deterioration is uncommon with zinc[278,300] but may occur.[310] Elevation in serum lipase or amylase may occur with zinc treatment for WD, without clinical or radiologic evidence of pancreatitis. Zinc may be utilized in patients with impaired renal function when therapy with chelation requiring urinary copper excretion might be ineffective.

Although zinc is currently reserved for maintenance treatment of WD, it is used as first-line therapy, most commonly for asymptomatic patients. It appears to be equally effective as D-penicillamine but much better tolerated.[278,311] Reports of large series of adults with WD indicate good efficacy,[299,310,312,313] possibly better in those with neurologic WD. In children with mild or asymptomatic WD, zinc treatment as primary therapy appears to be effective,[314–316] although some express caution.[306] Some individuals with severe disease were reported as doing well on zinc monotherapy.[314,317] "Combination" treatment with trientine plus zinc or D-penicillamine plus zinc has been advocated as treatment for severe disease: each is given at widely spaced intervals during the day, never simultaneously (see detailed discussion under "Decompensated Cirrhosis").

Dosing is in milligrams of *elemental* zinc. For larger children and adults, 150 mg/day is administered in three divided doses. It must be taken at least twice daily to be effective.[312] The actual salt used does not appear to make a difference with respect to efficacy as measured by the percent reaching goals for urinary copper excretion and normalization of serum ALT[304] but may affect individual tolerability. For smaller children <50 kg in body weight, the dose is 75 mg/day in three divided doses.[318] The dose is not well defined for children who are less than 5 years-old; however, 50 mg/day in two divided doses has been postulated,[318] similar to a weight-based dose.[319] Taking zinc with food interferes with zinc absorption[320] and treatment effectiveness.

Treatment targets

Adequacy of treatment with zinc is judged by clinical and biochemical improvement and by measuring 24-h urinary excretion of copper, which should be <100 μg (<1.6 μmol)/24 h on stable treatment. ALT normalization may be a good marker of effective treatment and positively correlates with the maintenance of 24-h urinary copper excretion below this threshold of 100 μg/24 h.[304,310] Additionally, elevated NCC normalizes with effective treatment; the estimated NCC may indicate this normalization.

Zinc lacks efficacy in a subset of patients with WD, but it is impossible to identify these patients