

# Zinc Maintenance Therapy for Wilson Disease: A Comparison Between Zinc Acetate and Alternative Zinc Preparations

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We evaluate Wilson disease (WD) treatment with zinc acetate (U.S. Food and Drug Administration approved) and alternative zinc salts. Studies examining zinc therapy in WD are few, and data on alternative zinc salts are limited. We describe one of the largest recent studies of zinc therapy in WD. First, we conducted a single-center retrospective review of 59 patients with WD (age 6-88 years, 32 female patients) treated with zinc (50-150 mg) for 0.8 to 52 years (median, 26 years); most were on prior chelation therapy (n = 39). Second, we developed a survey to explore patients' zinc therapy experience. Primary endpoints were alanine aminotransferase (ALT) and urine copper excretion ( $\mu\text{g}/24$  hours). Urine copper was categorized as low  $<25$   $\mu\text{g}$  (possible overtreatment), target 25-100  $\mu\text{g}$ , or elevated  $>100$   $\mu\text{g}$  (possible noncompliance or treatment failure). The target range was reached in 81% of patients on zinc acetate, 73% on zinc gluconate, and 57% on alternative zinc. Low urine copper was not associated with a high ALT. ALT was normal in 77% of patients with target urine copper but only in 16% with urine copper  $>100$   $\mu\text{g}$ . ALT elevations were not significantly different between zinc salts (Kruskal-Wallis,  $P = 0.26$ ). Our survey demonstrated the mean age of starting zinc was 26.8 years (3.5-65 years); most were treated with zinc acetate (45%) and zinc gluconate (42%). Before zinc treatment, 45% of patients were symptomatic; the majority of patients (80%) were asymptomatic on zinc. Gastrointestinal side effects were the predominant reason for changing zinc salts (38%), but most reported no side effects on current zinc therapy (67%). **Conclusion:** Effective treatment with zinc is possible in many patients with WD. The potential for treatment failure suggests close monitoring and consideration of alternative treatments are paramount for those without both a normal serum ALT and appropriate urine copper excretion. (*Hepatology Communications* 2019;3:1151-1158).

Wilson disease (WD) is an inherited disorder of copper metabolism in which copper accumulates and causes toxicity, the liver and brain being the most copper-sensitive organs. Medical therapy for WD is lifelong. The introduction of effective oral treatments began with the chelating agents d-penicillamine and trientine, which mobilize copper by increasing urinary copper excretion.

Later, zinc salts, which act by blocking dietary copper absorption, were found to be useful for the treatment of WD.

Treatment of patients with WD with zinc sulfate was initially proposed by Shouwink et al.<sup>(1)</sup> based on its de-coppering potential in sheep. The initial salt used in these studies was zinc chloride, which was abandoned as treatment due to gastric

*Abbreviations:* ALT, alanine aminotransferase; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; ULN, upper limit of normal; WD, Wilson disease.

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irritation; however, other zinc salts, such as zinc sulfate and zinc acetate, were then tested, which led to their clinical use for treating WD.<sup>(2-4)</sup> It was later discovered that zinc acts by inducing the synthesis of the endogenous metal chelating peptide metallothionein in enterocytes.<sup>(5-7)</sup> Metallothionein is a mainly cytosolic protein with a higher binding affinity for copper than zinc, and when copper is taken up by enterocytes, the copper replaces zinc on the metallothionein peptide.<sup>(8)</sup> When high levels of metallothionein are induced in intestinal cells by zinc, copper absorption is inhibited.<sup>(9)</sup> Nonabsorbed intestinal copper from the diet is eliminated along with copper in enterocytes (on the metallothionein peptide) when they are shed into the intestinal lumen and both are excreted into feces. This leads to the negative copper balance necessary for detoxification of the excess injurious copper within the liver and other tissues. Zinc can also induce metallothionein synthesis in the liver, leading to further neutralization of toxic copper.<sup>(9,10)</sup>

In 1997, the U.S. Food and Drug Administration (FDA) approved the use of zinc acetate for maintenance therapy for WD on the basis of studies over a 15-year period, including a long-term follow up study of 141 patients who received only zinc as maintenance therapy for WD. Brewer et al.<sup>(2)</sup> used copper balance studies that measured the absorption of radiolabeled <sup>64</sup>Cu added to a study diet and found that 25 mg of zinc acetate administered 3 times daily or 37.5 mg zinc acetate given twice daily was likely to be the minimum effective dose of this zinc salt for human use. Once daily administration of 75 mg was found not to be as effective as divided doses. This may indicate that in order to sustain adequate intestinal metallothionein induction, a dosage regimen of twice daily is the minimum necessary. The standard adult dosage that was

approved by the FDA following these studies was 50 mg 3 times daily, providing a margin of safety so that even if one dose was missed or taken ineffectively with food, dietary copper absorption would be effectively blocked. Recommendations were to give zinc acetate at least 30 minutes before or 2 hours after meals. For children <50 kg in weight, the recommended dosage was 25 mg taken in three divided doses.<sup>(11)</sup> For patients on zinc treatment, Brewer et al. suggested that the efficacy of zinc acetate treatment for WD be assessed by a goal of 24 urine copper values of <125 µg/day, and he recommended measurement of urine zinc values to assess for compliance. Others have suggested lower 24-hour urine copper cutoffs than the 125 µg/day proposed by Brewer and colleagues to ensure better copper control.<sup>(11)</sup>

Zinc treatment is associated with few side effects. The most common side effect of zinc treatment is gastric irritation, which sometimes may be helped by concomitant intake of protein or use of proton pump inhibitors. Occasionally, irritation can be severe, resulting in erosions and ulcers.<sup>(11,12)</sup> Other side effects that occur rarely include biochemical pancreatitis, resulting in elevated pancreatic enzymes (lipase/amylase) without clinical symptoms.<sup>(11)</sup> With long-term use, issues of overtreatment and zinc-induced copper deficiency can occur. This typically presents with anemia, neutropenia, as well as neurologic symptoms, including sensory or motor sensory neuropathies and myelopathies, which normally reverse with correction of the deficiency.<sup>(13)</sup>

Although zinc acetate is the only zinc salt in the United States that is currently FDA approved and in Europe, Wilzin is similarly a European Medicines Agency-approved zinc acetate preparation, there are several zinc salts available to patients as dietary supplements, including zinc sulfate, zinc gluconate,

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and zinc picolinate. The most recent European Association for the Study of the Liver guidelines for WD do not provide a clear recommendation on which zinc salt to use. Some patients have gravitated to alternative zinc salts due to issues of intolerance to zinc acetate, mostly due to gastric upset. Others have had issues of health insurance coverage for zinc acetate and have purchased their zinc over the counter using their own funds. Nevertheless, there are limited data on whether these alternative zinc salts are effective for treatment of WD. Our study aims to examine the maintenance treatment of WD with zinc acetate or different zinc salts to determine whether these alternative zinc preparations are as effective for the treatment of WD.

## Participants and Methods

A retrospective review of data from 59 patients with WD from one U.S. center (age 6-88 years, 32 female patients) treated with zinc for 8 months to 52 years (median, 26 years) was conducted. Thirty-nine patients were on prior chelation therapy. The primary endpoints for our retrospective review study included 24-hour urinary copper excretion and serum alanine aminotransferase (ALT).

Zinc formulations used by patients included acetate ( $n = 32$ ), gluconate ( $n = 22$ ), or alternative zinc preparations ( $n = 9$ ), with total daily doses of zinc ranging from 50 to 150 mg. The majority of patients were on the recommended daily adult dose of 150 mg total elemental zinc given in divided doses ( $n = 50$ ); of those on a reduced dose, 7 patients were children. Other reasons for a reduced dose ( $n = 7$ ) were based on side effects and laboratory results indicating overtreatment. Treatment efficacy was assessed by 24-hour urine copper excretion and serum ALT obtained from patient data <6 months apart. Nonceruloplasmin copper (NCC) was also calculated.<sup>(11)</sup> Data analysis was performed on patients with all data points available. Those without both ALT and 24-hour urine copper results within this time frame were excluded from analysis. Gastrointestinal (GI) absorption of ingested zinc was assessed with a 24-hour urinary zinc measurement, and comparisons were made between different zinc dosages. Adverse effects to medication and reasons for changes in WD treatment were obtained from the medical record.

Our retrospective record review was supplemented with a Health Insurance Portability and Accountability Act of 1996-approved online Qualtrics survey tool. Out of our study cohort, we were able to contact 56 subjects. Survey questions were designed to explore patients' WD treatment history and experience using different zinc preparations as therapy in WD. Subjects were given a unique study number and were sent a personal link to complete the survey. The survey remained active for a 2-month period before closing.

## Results

Zinc formulations examined in our retrospective review included acetate ( $n = 32$ ), gluconate ( $n = 22$ ), or alternative zinc preparations ( $n = 9$ ), with total daily doses ranging from 50 to 150 mg. In our cohort, presentations were divided into asymptomatic ( $n = 12$ ), hepatic ( $n = 25$ ), neurologic ( $n = 8$ ), and combination ( $n = 15$ ) based on narratives from physician notes.

For the online survey, 31 of 56 patients contacted completed the survey. The survey confirmed that more than half of patients contacted were taking nonprescription zinc, with 29% purchasing their zinc online and 22% using nonprescription over the counter zinc formulations. The majority of patients were on zinc acetate (45%) followed by zinc gluconate (42%). Other preparations included zinc sulfate and zinc picolinate. The mean age of the survey study cohort at diagnosis was 18 (range, 2-43 years). The average age of starting treatment with zinc was 26.7 years (range, 3.5-65 years). All patients were on zinc treatment for more than 6 months (range, 0.6-35 years; median, 26 years).

## URINE COPPER EXCRETION AND LIVER TESTS ON ZINC THERAPY

Urinary copper excretion ( $\mu\text{g}/24$  hours) was categorized as low <25  $\mu\text{g}$ , target range 25-100  $\mu\text{g}$ , or elevated >100  $\mu\text{g}$ <sup>(11)</sup> (Table 1). Levels >100  $\mu\text{g}/24$  hours suggest possible treatment failure or noncompliance with medication or diet, while levels <25  $\mu\text{g}/24$  hours may indicate overtreatment. Target 24-hour urine copper was present in 81% of patients on zinc acetate, 73% on zinc gluconate, and 57% on alternative zinc. To account for data obtained from hospital and different commercial laboratories, results for ALT were

**TABLE 1. RELATIONSHIP BETWEEN 24-HOUR URINE COPPER AND SERUM ALT RESULTS FOR ZINC ACETATE, ZINC GLUCONATE, AND ALTERNATIVE ZINC PREPARATIONS**

Urine copper ( $\mu\text{g}/24$ hours)		Zinc Acetate (n = 26)			Zinc Gluconate (n = 19)			Alternative Zinc (n = 7)		
		<25	25-100	>100	<25	25-100	>100	<25	25-100	>100
ALT	Normal	2 (8%)	16 (61%)	0	2 (11%)	12 (63%)	1 (5%)	2 (29%)	3 (43%)	0
	1-2 $\times$ ULN	0	5 (19%)	0	0	2 (11%)	0	0	1 (14%)	1 (14%)
	2-3 $\times$ ULN	0	0	1 (4%)	0	0	0	0	0	0
	>3 $\times$ ULN	0	0	2 (8%)	0	1 (5%)	1 (5%)	0	0	0

expressed as less than the upper limit of normal (ULN) or a multiple of the ULN for the laboratory performing the testing (1-2, 2-3, or >3 times the upper limit of ALT). Patients were divided into groups based on their response to treatment with respect to ALT and 24-hour urine copper (see Table 1). No patient with low urine copper had a high ALT. ALT was normal in 77% of patients with a target range urine copper of 25-100  $\mu\text{g}/24$  hours; however, when urine copper was >100  $\mu\text{g}/24$  hours, ALT was normal in only 1 patient (16%). ALT was elevated in 31% of patients on zinc acetate, 21% on zinc gluconate, and 28% on alternative zinc. The majority (3 of 4) patients with liver tests >3 times ULN also had an elevated urine copper >100  $\mu\text{g}/24$  hours. Notes of patients with both an elevated 24-hour urine copper and ALT were reviewed. Only 1 of 5 patients was noted by the treating physician to have compliance issues; the rest were documented to be adherent to treatment.

Although NCC was calculated in patients in this study using data from commercial assays (data not shown), 47% of patients had values of 0 or negative results, making these values uninterpretable and suggesting that urine copper and serum ALT are better markers for monitoring most patients on zinc therapy.

## ADHERENCE AND ABSORPTION

Urine zinc excretion is a helpful tool in evaluating both absorption and compliance with zinc therapy. In patients taking zinc therapy, urinary zinc is increased, indicating intestinal absorption of the zinc. We reviewed urine zinc excretion for the different zinc salts and the specific daily dose of zinc. The 24-hour urine zinc excretion ( $\mu\text{g}/24$  hours) for specific total daily zinc dose included zinc acetate at 50 mg (n = 2; median, 1,271; range, 823-1,720), 75 mg (n = 6; median, 2,298; range, 907-3,523), and 150 mg

(n = 12; median, 3,220; range, 725-6,487); zinc gluconate at 100 mg (n = 1; 1,361), and 150 mg (n = 13; median, 3,056; range, 833-8,661); and other zinc salts at 75 mg (n = 1; 1,200) and 150 mg (n = 2; median, 6,318; range, 2,591-10,045).

We supplemented these results using our survey study to explore when patients were taking their zinc to ensure that this was consistent with good absorption. Our survey demonstrated that only 1 person reported taking zinc incorrectly directly after food. The rest of the patients reported taking zinc appropriately, with 45% of patients taking zinc before meals, none with food, and 8 patients a few hours after. Other patients (25%) did not take zinc consistently at the same time of day but did use zinc appropriately either 1 hour before or 1-2 hours after a meal.

Graphs in the Supporting Material demonstrate the relationship between urinary zinc excretion and urinary copper excretion and the relationship between urinary zinc excretion and serum ALT. On reviewing results of urine zinc and urine copper, there were only two results that were >100  $\mu\text{g}/24$  hours; these were associated with a raised ALT (just over 1 time and 2 times ULN). We speculate that the increased copper excretion may be related to an effect of zinc on renal tubular function and resulting increased excretion.<sup>(14)</sup> The clinical significance of this is difficult to interpret as there were only two results where urine copper measurements were high. As the study is retrospective, not all subjects had the required data sets; therefore, caution is necessary when interpreting trends. Only limited data were available for which paired urine samples were available and where an ALT blood test was done within 6 months of the urine zinc test. A future prospective evaluation of this would be useful for validating results.

## IMPROVEMENT IN SYMPTOMS ON ZINC TREATMENT

Our online patient-completed survey demonstrated that there was an almost equal distribution of patients that were asymptomatic (54%) and symptomatic (45%) before starting treatment with zinc. Of those that were symptomatic before treatment, 45% had neurologic symptoms, 25% presented with signs or symptoms of liver disease, and 20% with mental health issues. The majority (80%) reported no ongoing symptoms on treatment with zinc. Five of the 7 patients that remained symptomatic had ongoing neurologic symptoms, 1 person had ongoing liver symptoms, and 1 person had ongoing mental health issues, supporting previous studies that established neurologic symptoms may have the least reversibility. No patients reported worsening symptoms. Although the data are qualitative, they suggest that while some patients may not respond as effectively based on their biochemical data, this did not translate clinically into deterioration in symptoms.

## UNWANTED EFFECTS OF ZINC

In our retrospective record review, 5 patients were switched from zinc acetate to alternative zinc salts due to GI side effects and 1 on current zinc acetate therapy noted GI symptoms. Four patients on zinc gluconate had nausea/dyspepsia, and 3 patients were anemic. Neutropenia was absent in patients with urine copper <25 µg/24 hours, suggesting no clinically relevant copper deficiency.

Our survey demonstrated similar results. The majority of patients reported no side effects on current zinc therapy (68%). Patients that had previously been on a different zinc preparation (38%) changed to an alternative zinc salt mainly due to GI side effects. The majority changed from zinc acetate (n = 11, 57%). Of these 11 patients, 4 changed due to gastric side effects related to nausea or upset stomach, 1 due to a skin reaction, 5 were changed due to physician recommendation, and 1 because of cost. Four patients taking zinc gluconate changed due to gastric side effects, 1 due to physician recommendation, and 1 because of swallowing difficulties. One patient on zinc sulfate changed due to upset stomach. While the majority of patients experiencing gastric side effects on a previous zinc

salt had improved gastric symptoms on their current zinc salt, 1 patient still had gastric side effects and 1 patient tried three different zinc salts before finding one that was tolerable. Results suggesting which salt was the most tolerable are not conclusive from this study.

## TREATMENT CHANGES TO ZINC

Our survey explored treatment changes in patients not initially on zinc salts exclusively. Most patients (80%) had been on another treatment or combination treatment (chelator and zinc salt) before starting zinc therapy. The majority of patients were previously on d-penicillamine, followed by trientine, and then combination therapy of one of these chelators and zinc salts. Other treatments included British anti-Lewisite (BAL) injections (or dimercaprol) and treatment with sodium tetrathiomolybdate and zinc. Most patients (47.6%) that were previously treated with d-penicillamine switched to treatment with zinc due to side effects that included allergic reactions (hives), knee pain, skin wrinkling, and proteinuria. In 33% of patients, this was a physician-recommended change. Other reasons (n = 3) included personal preference, surgery, and joining a zinc clinical trial.

The majority of patients previously on trientine reported that they were changed from treatment due to physician recommendation (36%); in addition, 31% of patients had experienced side effects on trientine (diarrhea, joint pains, lupus reaction, possible colitis, rising liver tests, worsening symptoms), 9% switched due to personal preference, and other reasons included pregnancy and insurance coverage. All patients on previous combination therapy with a chelator and zinc were transitioned to zinc monotherapy due to physician recommendation.

## Discussion

We aimed to compare the effectiveness of zinc acetate to different salts of zinc for the treatment of WD. We examined the combined retrospective data from our cohort from a single center, supported by supplementary data from an online patient-completed survey study. Overall, our results indicated that alternative zinc preparations in addition to the already approved zinc acetate may be an effective treatment

option for WD, with good absorption in many but not all patients. Moreover, in analyzing our data, we were able to investigate how best to evaluate and monitor these patients on zinc therapy for effectiveness of their WD treatment.

The effectiveness of zinc treatment is dependent on the zinc moiety being absorbed into enterocytes. A marker of absorption of orally administered zinc in humans by enterocytes is the urine excretion of zinc. One issue that has been raised previously is that there may be differences between zinc salts with respect to their absorption, and this could affect their ability to block copper absorption. In our study, due to the retrospective nature and inclusion of patients seen at our center but who may have been prescribed zinc by other providers, there was not a single consistent dosage of zinc or type of alternative zinc used. However, the majority of patients in our cohort using alternative zinc salts were using zinc gluconate. The absorption of zinc gluconate appeared to be similar to that for zinc acetate for patients using the recommended daily total dose of 150 mg (in divided doses). As expected, for each of the zinc salts, the mean absorption as estimated using urine zinc excretion was dose dependent and increased as the total daily dose of the zinc increased.

Urinary copper excretion below 100  $\mu\text{g}/24$  hours was a primary endpoint for this study.<sup>(11)</sup> The majority of patients on zinc acetate and zinc gluconate achieved this therapeutic goal for 24-hour urine copper excretion. In the majority of patients, a high urine copper excretion above 100  $\mu\text{g}/24$  hours was associated with a raised serum ALT level. Only 1 of 6 patients with a urine copper excretion  $>100$   $\mu\text{g}/24$  hours had a normal ALT level.

The second endpoint we used for this study was ALT as a surrogate marker for liver injury due to untreated WD. A retrospective study by Weiss et al.<sup>(15)</sup> compared the results of zinc treatment to chelation therapy. Hepatic treatment failure was defined as an increase in liver enzymes (aspartate aminotransferase, ALT, and gamma-glutamyltransferase)  $>2$ -fold ULN or 100% of baseline with an increase in urinary copper excretion. Similarly, we chose to analyze the patients in this study for treatment success based on the same parameter of ALT being normal or  $<2$  times ULN. In our study, most patients on all preparations of zinc had a normal ALT; however, ALT was elevated in 34% on zinc acetate, 21% on zinc gluconate,

and 28% on alternative zinc. ALT results were not significantly different among the different zinc salt treatment groups (Kruskal-Wallis test,  $P = 0.26$ , not significant at  $P < 0.05$ ). ALT was elevated in 6/26 (23%) patients on zinc acetate without an elevated 24-hour urine copper, in 3/19 (16%) on zinc gluconate, and 1/7 (14%) on alternative zinc salts. As this study was limited to a cross-sectional analysis, we do not know whether the abnormal testing noted in some patients would ultimately lead to liver injury or liver failure. However, we postulate that this is a good endpoint based on studies of other chronic liver diseases, such as autoimmune hepatitis, where guidelines for treatment of that disorder included a target of normal transaminases as data suggest that when this is achieved, patients do not have further disease progression relative to those that do not normalize transaminases on therapy.<sup>(16)</sup> Whether WD behaves similarly to autoimmune hepatitis with respect to the ALT target is an unanswered question, and longitudinal data are needed to demonstrate this outcome.

In our literature review, we did identify cases of WD where treatment goals were not reached on zinc therapy, some with significant consequence. It should be noted that in Brewer et al's original studies submitted to the FDA for approval of zinc acetate, efficacy was not 100%.<sup>(17)</sup> Linn et al.<sup>(18)</sup> described long-term exclusive zinc sulfate monotherapy in 17 symptomatic patients. While most patients with hepatic disease improved, 2 progressed and decompensated; 2 patients with exclusively neurologic presentations of their WD developed liver disease on zinc, and 2 with hepatic presentation of WD developed mild neurologic symptoms. In another study of 26 asymptomatic patients with WD with abnormal ALT levels, 9 patients demonstrated slow or no response to zinc gluconate therapy based on ALT levels remaining high or deteriorating. While no clinical deterioration was seen in a French study of pediatric patients with WD,<sup>(19)</sup> 9 children received zinc acetate alone as first-line treatment. Two of these 9 patients were switched to d-penicillamine due to failure to achieve normal transaminases. Of the 12 children who received zinc maintenance after d-penicillamine, all remained well controlled but 2 were switched to trientine because of zinc-related side effects.<sup>(20)</sup> A retrospective study on zinc monotherapy in patients with WD with mild liver disease diagnosed in childhood demonstrated that of the 15 initially treated with zinc, there were

2 nonresponders, both of whom were found to have complied poorly with treatment as witnessed by inadequate levels of serum and urinary zinc and/or copper excretion.<sup>(21)</sup>

The retrospective review by Weiss et al.<sup>(15)</sup> was one of the few that compared the long-term outcome of treatment with chelation and zinc. Treatment discontinuation due to treatment failure, liver transplantation, or death was seen in 18 of their 88 patients on zinc therapy. Although treatment with chelating agents or zinc was effective in most with WD, it was felt that chelating agents were better at preventing hepatic deterioration.<sup>(15)</sup> Therefore, it is important to know that zinc treatment is effective for patients with WD who are on this therapy. Monitoring to identify nonresponders to zinc therapy for WD as early as possible is therefore particularly important as is exploring compliance with treatment as a factor contributing to treatment failure. Based on our data, we would begin further exploration of efficacy for those zinc-treated individuals without a normal ALT and urine copper excretion of <100 µg/24 hours. While we agree that a raised ALT may indicate ineffective treatment for WD, particularly when associated with raised 24-hour urine copper excretion, alternative causes for liver injury need to be screened for. These include independent causes of liver injury, such as fatty liver disease, drug- or alcohol-induced liver injury, viral hepatitis, or autoimmune disease. In these individuals with persistent abnormalities of transaminases and the possibility of hepatic synthetic dysfunction as well, serologic studies, imaging, and even liver biopsy may prove helpful in evaluating for secondary liver disease. A previous study by Wong et al.<sup>(22)</sup> investigated the clinical epidemiology of WD in patients with concurrent liver disease. Of 42 patients with WD, 9 patients had comorbid liver disease; these had greater evidence of cirrhosis at presentation and showed greater mortality, highlighting the importance of detecting coexistent disease at an early stage.

There are some limitations to our study. While the results indicate that effective treatment with alternative zinc preparations is possible, the retrospective nature of the study and the relatively small numbers due to the rarity of the condition limit the strength of the conclusions that can be drawn with respect to differences between zinc acetate and other zinc salt therapy for WD. In addition, certain results may be related to selection bias of patients seeking help at a

tertiary referral center. A prospective trial with standardized evaluation, dosing, and monitoring would strengthen the evidence base. Furthermore, longitudinal follow-up of patients on therapy would allow for evaluation of endpoints of treatment efficacy and failure and patient survival and possible changes in hepatic fibrosis.

In conclusion, some patients with WD can be treated effectively with alternative zinc preparations or with zinc acetate; however, the potential for treatment failure in some suggests close monitoring is paramount for patients on zinc therapy. Irrespective of the zinc formulation used, treatment efficacy relies on appropriate dosage, tolerability, and compliance. Treatment monitoring while on zinc therapy should include 24-hour urine copper and zinc excretion and serum ALT. Parameters determining treatment failure of zinc for WD need to be more clearly defined so that patients may be considered for alternative treatment in a timely fashion before disease or symptom progression occurs. However, longitudinal prospective studies with standardization of evaluation, dosing, and monitoring and head to head comparison with chelation agents are still needed to provide a robust evidence base for the optimization of medical therapy for WD. These studies could have global implications on the use of zinc preparations for WD, particularly due to its wide accessibility in developing and nondeveloping countries. With the high cost of currently available oral chelating agents, an understanding of the potential utility of the different zinc preparations will be of even greater benefit in expanding and optimizing treatment options for patients with WD.

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## Supporting Information

Additional Supporting Information may be found at [onlinelibrary.wiley.com/doi/10.1002/hep4.1384/supinfo](http://onlinelibrary.wiley.com/doi/10.1002/hep4.1384/supinfo).