The Modern Treatment of Wilson's Disease

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Abstract

Wilson's disease is an inherited defect in biliary copper excretion, causing a buildup of copper and copper toxicity, primarily in liver and brain. Presentation with liver disease and/or neurological disease usually occurs in the second and third decades of life. Recognition of the disease is often delayed, which is unfortunate, because once appropriate treatment is started, progression of the disease can be halted, and further damage avoided. Regarding current treatment, many physicians are only aware of penicillamine, because it was the first orally effective drug developed. However, penicillamine has outlived its usefulness, being more toxic than more recently developed drugs. For the hepatic presentation, a combination of trientine and zinc should be used for 4-6 months, then trientine stopped and zinc used for lifelong maintenance therapy. For the neurological presentation, tetrathiomolybdate should be used if available for 8-16 weeks, then zinc for maintenance. If tetrathiomolybdate is not available, zinc should be used. For presymptomatic patients, zinc should be used from the beginning. Zinc should also be used for pregnant and pediatric patients, with a reduced dose for the latter. Zinc causes gastric intolerance in some patients, so in all cases where zinc is the favored therapy, if it is not tolerated, then trientine should be used as second choice. In too many cases, patients are put on zinc, compliance not monitored, and then papers are written about "zinc failures". There are no zinc failures, just noncompliance problems.

Keywords: Wilson's disease; Penicillamine

Introduction

Treatment of Wilson's disease (WD) is important because the disease can be halted, and irreversible damage prevented. Since the disease is due to copper accumulation and copper toxicity, the useful drugs are called anticopper drugs. In the beginning, the only anticopper drug was penicillamine, and a generation of WD patients owe their lives to treatment with penicillamine. But a generation of physicians learned only the use of penicillamine in the treatment of WD. Now, additional drugs are available, and it is critically important that they be used, rather than penicillamine, especially for certain phases of the disease. Penicillamine should be used only rarely for the treatment of WD. It has too many side effects, it makes many neurologically presenting patients permanently worse, and there are now alternative drugs with excellent efficacy. Second, tetrathiomolybdate is by far the optimal drug for treating the neurologic presentation, but it is not yet approved, and must be obtained from compounding pharmacies. This needs to be remedied. Third, zinc is the treatment of choice for many phases of WD, including maintenance therapy, treatment of the presymptomatic, pregnant and pediatric patients, and in the absence of tetrathiomolybdate, treatment of the neurologic presentation. But too many physicians are not using zinc properly, and then inappropriately claiming there are "zinc failures". This paper will educate physicians and others on the correct modern treatment of Wilson's disease.

Wilson's disease is, of course, an orphan disease, with an estimated 10,000 patients or thereabouts, in the U.S. Fortunately, it is one of the few orphan diseases where very good treatments are available. However, it is important that the disease be recognized and treated early in the course, before copper accumulation, the cause of the disease, does excessive and irreversible damage.

Brief Review of the Disease

Wilson's disease is an autosomal recessive inherited disease of copper accumulation and copper toxicity [1-7]. Copper balance is maintained in the body by the hepatic excretion of excessive copper in the bile, for loss in the stool. In WD patients, there is mutation of the ATP7B gene [8-10], a copper binding ATPase enzyme, involved in the biliary excretion of copper. Both copies of the ATP7B gene have to have disabling mutations to cause the disease. Heterozygous carriers of one mutated gene accumulate some extra copper, but not enough to require treatment, hence the disease is called recessive.

In general, people take in an average of about 1.0 mg copper per day. This is an excess of about 0.25 mg/day. In WD, with the biliary excretion mechanism disabled, this small amount of excess copper accumulates every day of their lives, with storage occurring in the liver. Gradually, the storage capacity of the liver is exceeded, and liver damage begins to occur. In the late teenage years or twenties, the patient may present with clinical liver disease. This may manifest itself as hepatitis, with or without jaundice, and with elevated liver transaminase enzymes, ALT, AST, and GGT. If not diagnosed, the hepatitis may go into remission only to reoccur later. This pattern is often misdiagnosed as chronic relapsing hepatitis, with an implication of viral or autoimmune etiology.

Alternatively, the patient may first present because they have developed cirrhosis, and present with one of the complications of cirrhosis, such as liver failure with ascites and edema, a bleeding diathesis from low clotting factors and a low platelet count, or bleeding from gastric or esophageal varices. While the second and third decades

of life are the most common ages of presentation, the time of presentation can be quite broad, and extend into the 70s in rare cases [11].

Occasionally patients may present with fulminant hepatic failure with hemolysis. The cause of the hemolysis is the release of large amounts of copper into the circulation by dying liver cells, which damages erythrocytes. The association of liver failure with hemolysis is almost always due to Wilson's disease.

About half the patients do not present clinically with liver disease, although they all have underlying liver disease, but present clinically with neurologic disease due to copper overflow from the liver and accumulation in the brain. The primary parts of the brain affected are the basal ganglia and other areas that coordinate movement; hence the neurologic disease is a movement disorder. The main abnormalities are tremor, dystonia, and incoordination with speech, swallowing and movements of fingers, hands, and limbs often affected. Posture may become so affected such that the body and limbs assume grotesque positions. Again, presentation is usually in the second and third decades of life, but may be later in some cases.

As mentioned earlier, it is important to recognize, diagnose and treat the disease as early as possible, because some of the copper damage becomes irreversible. Treatment with anticopper drugs is very efficient at halting further progression, but may not reverse all the damage already done. If the patient is not diagnosed and treated, the disease is fatal.

There are a number of tests one can use to make the diagnosis of WD. A good one is 24 hour urine copper. It is almost always elevated over 100 µg in symptomatic patients (normal is 50 µg or less). False positive elevated urine copper can occur in obstructive liver diseases. Blood ceruloplasmin (Cp) is generally low in WD because the ATP7B protein also helps in incorporation of copper into the Cp molecule before it is secreted into the blood by the liver. Without copper, the apoCp is soon removed from the circulation. So Cp is generally quite low in WD, but in about 10% of patients it isn't low [6], and in about 10-15% of carriers, Cp is low. So low Cp levels can be used as an indication of WD, but are not a definitive diagnostic test. It is somewhat more reliably low in the neurologic presentation. Serum copper assay is not very useful because it generally reflects the low Cp level, since copper in Cp accounts for most of serum copper. Copper accumulation in rings in the cornea of the eye, called Kayser-Fleischer (KF) rings after their discoverers, are an excellent diagnostic feature in the neurologic presentation, being present at least 99% of the time [6]. KF rings are also present most of the time in the hepatic presentation [3]. They can be detected definitively only by slit lamp examination by an ophthalmologist. The usual definitive test for diagnosis of Wilson's disease is a liver biopsy and quantitative assay of liver copper. In WD, liver copper is always over 200 µg/g dry weight tissue (normal, 50 µg or less). Again false positives can occur in obstructive liver disease.

DNA mutation detection is being increasingly used as a diagnostic test. The problem is that several hundred disabling DNA mutations are known. Many patients are composite heterozygotes for two different mutations. It is necessary that the DNA test be able to detect all the mutations present in a population, and be able to identify the presence of two mutations in composite heterozygotes. This makes this kind of testing difficult.

A special class of patients are called presymptomatic. These are generally discovered by family workups. Since the disease is autosomal recessive, every full sibling of an affected patient has a 25% risk for having the disease. Full siblings deserve rigorous workups, because if they are diagnosed at the presymptomatic stage, prophylactic anticopper treatment can prevent them from having any problems from the disease. Since the disease is 100% penetrant, they are certain to have symptomatic liver and/or brain disease if not treated prophylactically. In these patients, urine copper is diagnostically elevated only about half the time, and KF rings are present only about one third of the time. However, liver copper is always diagnostically elevated. Also in this case, DNA analysis really comes to the fore. By genotyping certain markers around disabled ATP7B genes in the affected sibling, other siblings can clearly be genotyped as having two (affected), one (carrier), or none (clear) disabled genes.

The Anticopper Drugs

The term "anticopper drugs" is preferred for the drugs used to control copper in WD. Some use the term "copper chelators", but only two of the drugs, penicillamine and trientine are copper chelators. The other two, zinc and tetrathiomolybdate work by other mechanisms.

We will discuss anticopper drugs in the sequence of their discovery, not in the order of their priority. When it was discovered WD was due to copper toxicity attempts were made to come up with some type of agent to counter or remove the copper. An early agent was British antilewisite (BAL). But BAL had to be given by injections which were often painful. As the effective oral drug, penicillamine, was developed, BAL fell into disuse. Occasionally, someone recommends its use even now, usually in difficult cases, thinking it had some special helpful property, but this is inappropriate. Anything BAL can do, oral anticopper drugs can do better.

Penicillamine: The anticopper drugs used in WD are listed in Table 1. Penicillamine was the first orally effective anticopper drug, and was introduced by Walshe in 1956 [12]. It acts by chelating copper and increasing copper excretion in the urine. It is usually given 1.0 g/day in two divided doses, away from food. If given to a previously untreated patient, it usually results in 1-2 milligrams of urinary copper excretion per day. For reference, normal urinary copper is up to 50 µg/day, and untreated WD patients may excrete 100-250 µg/day. Normal dietary intake of copper is about 1.0 mg/day, so the impact of penicillamine is to produce a large negative copper balance. As therapy proceeds, urinary copper gradually decreases, as the excess of easily mobilizable copper of the body is slowly decreased. After 6-12 months of penicillamine therapy, 24 hour urine copper may be down to 0.75-1.5 mg. There are still large excess stores of copper in the liver, but these are tightly bound, non-toxic, and only gradually reduced over years of anticopper therapy.

Drug	Mechanism Of Action	Recommended Use	Toxicity
Penicillamine	Chelator, urinary	None	Neurologic worsening, Acute hypersensitivity

	excretion of copper		Proteinuria Bone Marrow suppression Damage to collagen Damage to skin Trigger of autoimmune diseases
Trientine	Chelotor, urinary excretion of copper	Hepatic presentation with zinc, Second choice to zinc for many other types of patients	Proteinuria Bone Marrow suppression Trigger of autoimmune diseases Neurologic worsening
Zinc	Blockage of copper absorption	Maintenance, Presymptomatic, Pregnancy, Pediatric, Hepatic presentation with trientine, Second choice for neurologic presentation	Moderate gastic discomfort in 5-10% of patients
Tetrathiomolybdate	Complexor of copper with protein	Neurologic presentation	Reversible anemia Reversible further elevation of AST and ALT

Table 1: Anticopper drugs used in Wilson's disease therapy.

Penicillamine is completely effective in lowering copper levels and eliminating further copper toxicity over time. As a result, a whole generation of WD patients have benefitted from this efficacy. But the downside is that penicillamine has a large number of toxic side effects (Table 1). A large number of patients, perhaps 25%, have an initial hypersensitivity that has to be treated with steroids, or penicillamine stopped, and restarted at a very low dose, gradually building up to a therapeutic dose. During chronic use, there are large numbers of other side effects such as bone marrow suppression, immune modulated diseases, skin abnormalities, and connective tissue effects that may lead to aneurysms, etc. Further, if penicillamine is used in initial treatment of neurologically presenting patients, it makes 50% initially worse, and it makes a high percentage, perhaps 25% permanently neurologically worse, according to US studies [13]. Walshe and Yealland [14] found 22% of English patients deteriorating neurologically when initially treated with penicillamine. Kalita et al. [15] found 30% of Indian patients worsening neurologically from initial penicillamine therapy. This worsening probably occurs by mobilization of hepatic copper into the blood for excretion in the urine. During the blood elevation of copper, the brain copper is probably further elevated.

When penicillamine is used, it is important to also give the patient 25 mg of pyridoxine/day, unless it is part of the penicillamine formulation, otherwise the patient will become pyridoxine deficient. In the early stages of treatment, it is important to monitor frequency of side effects by measuring blood counts, blood biochemistries, and urinalysis especially for proteinuria. This should be done weekly at first, then after a month biweekly, after 3 months, monthly, after 6 months, quarterly after a year every 6 months, and after 2 years, if no side effects, annually. Similarly, patients should be seen at frequent intervals in the beginning, and then at increasing intervals later, to check the patient for side effects and compliance.

To monitor for efficacy with penicillamine treatment, the usual method is to follow 24 hour urine. This is straightforward early during treatment, to follow the gradual decline in urine copper as treatment proceeds. After a year or two of treatment, it becomes difficult to identify noncompliance, particularly if it is intermittent. Noncompliance leads to increase body loading of copper, which leads to increased urinary copper. But since penicillamine acts by increasing urine copper, it is hard to separate out the effects of the drug from a period of noncompliance. Some follow so called serum free copper to monitor. Blood copper is in two pools, the larger pool, 85-90%, bound to ceruloplasmin (Cp) which is safe, and the rest bound to albumin and various molecules, very mobilizable, called serum free copper, and very unsafe if this pool is expanded, as it is in untreated WD. To calculate serum free copper, Cp and serum copper are assayed. Each mg of Cp contains about 3 μg of copper so the mg/dl of CP, usually low in WD is multiplied by 3 and subtracted form the μg/dl of serum copper. If Cp is 5 mg/dl and serum copper is 30 μg/dl in a given patient, $5 \times 3=15$, subtracted from 30 gives 15 μg/dl of serum free copper. In WD, serum free copper should be kept at 25 μg/dl or below, to avoid further copper toxicity. This number can be followed, and if it starts going up, the physician should worry about noncompliance. However, this approach has considerable error, and is therefore not very precise.

Penicillamine is U.S. FDA approved for use in treating Wilson's disease without any restrictions regarding what phase of disease can be treated.

Trientine: Because of the toxicity associated with penicillamine, Walshe [16] later introduced trientine, another copper chelator (Table 1). Trientine is also given at about 1.0 g/day, again in two divided doses, and again should be separated from food. It is somewhat less robust than penicillamine in causing urinary excretion of copper, so that with initial therapy, 0.75 to 1.5 mg 24 hour urine copper is more typical. With 6-12 months of therapy, 24 hour urine copper may be down to 0.35 to 1.5 mg/day. Again, trientine is completely effective in lowering copper levels and eliminating further copper toxicity over time. It does share some of the same side effects with penicillamine, but at a considerably lower frequency (Table 1). Unfortunately, it does share penicillamine's propensity to cause neurological worsening if used as initial therapy in neurologically presenting patients. In one well-controlled study, the prevalence of neurological worsening was 26%, and those who worsened didn't do well with three out of six subsequently dying [17].

It is not necessary to use pyridoxine with trientine therapy, as it is with penicillamine. It is important to do some blood studies and urinalysis to monitor for side effects, although the frequency of monitoring doesn't have to be as rigorous, since side effects are less common. Also, early in treatment, the patient should be seen with some frequency, to monitor for side effects, and to follow 24 hour urine copper, and possible serum free copper. The monitoring of efficacy in trientine treated patients has the same problem as with penicillamine therapy, that is, increased body loading with copper increases urine copper, but since the drug acts by increasing urine copper, a period of noncompliance followed by taking the drug also causes an increased urine copper. So it is hard to sort out what is happening when urine copper increases. For this reason, serum free copper, calculated as covered in the penicillamine section, is often followed.

Trientine is U.S. FDA approved for use in treatment of WD patients who are intolerant of penicillamine. However, its current use is much broader than that, as will be obvious when we cover treatment of various phases of WD.

Zinc (Table 1): The first use of zinc in WD was by Schouwink [18] from the Netherlands as part of his thesis work. Unfortunately, other than the thesis, this work was never published. Hoogenraad and colleagues [19,20], also from the Netherlands, followed up Schouwink's work and gave additional WD patients zinc. Meanwhile, independently, Brewer's group in the U.S. had observed that zinc therapy for sickle cell patients produced copper deficiency, and initiated zinc therapy trials in WD patients [21-37]. They discovered that zinc blocks copper absorption through induction of intestinal cell metallothionein, which binds copper and prevents its transfer into the blood [31]. The blood copper is sloughed with the intestinal cells, which have about a 6 day turnover time, for excretion into the stool. The Brewer group discovered that zinc had to be given away from food to be effective, because substances in food bind zinc, and prevent its effect on the intestinal cells [21].

Because zinc was an orphan product, the Brewer group had to do all the things that a pharmaceutical company would normally do to develop a product. This included dose response [22,29,33], evaluation of possible side effects [26,30,34], and ways to monitor dose and efficacy [23,25]. Use during pregnancy was evaluated [37] and use in

pediatric patients [36]. Based on these data, zinc was approved for maintenance therapy on WD by the U.S. FDA in 1997, as Galzin. The recommended adult dose was 50 mg of elemental zinc three times/day, each dose separated from food and beverages other than water by at least one hour. It is important that 50 mg be the dose of elemental zinc, not the dose of the particular salt used. Most formulations will state the amount of elemental zinc on the bottle. The only significant side effect of zinc is gastric intolerance, that is, burning and epigastric discomfort that involves perhaps 10% of patients (Table 1). This can be mitigated by taking the first dose at midmorning, rather than before breakfast, and taking doses with a little bit of protein, which affects efficacy the least of all foods.

Because of lack of side effects other than gastric intolerance, it isn't necessary to do laboratory studies during initial treatment to monitor for zinc toxicity. Monitoring for efficacy with zinc therapy is very much easier and straightforward than it is for penicillamine and trientine. The reason is that zinc acts by increasing stool excretion of copper, and doesn't directly affect urine copper. Thus, the 24 hour urine copper becomes a good measure of body loading of copper. In a previously untreated patient, 24 hour urine copper may be 150-250 µg (normal is 50 µg or below). With zinc treatment this will gradually come down to 125 µg or below. This value should be kept at 125 µg or below to avoid further copper toxicity. In the beginning, it is good to monitor 24 hour urine copper every 3 months or so, to check on compliance. It is very useful to monitor the 24 hour urine zinc as well as copper levels. In a patient complying well with a therapeutic dose of zinc, 24 hour urine zinc should be at least 2.0 mg. If it falls below this, it is a good early screening warning for poor compliance. In a poor complying patient, this will occur a month or more before urine copper increases significantly. This is a wonderful tool to monitor compliance in zinc treated patients. The Brewer group had one badly noncomplying patient taking zinc only a week or two prior to his regular monitoring. Thus, the zinc value looked good, but urine copper was slowly increasing. Compliance is a major problem in WD, because therapy is life long, and many patients are young. Compliance may be more of a problem with zinc therapy than with other therapies because of the annoying gastric side effects of zinc in some patients. While these side effects are only very troublesome in 5-10% of patients, 40 to 50% of patients have occasional mild discomfort. This may act as a disincentive to take all of their zinc medication, or to take some of it too close to food ingestion. Zinc is U.S. FDA approved for the treatment of the maintenance phase of WD. As with trientine, its current use is much broader than that.

Tetrathiomolybdate: So far this drug is not U.S. FDA approved. But its use is so critical to the treatment of the neurological presentation, that it is described and its background given here (Table 1). Meanwhile, approval is being worked on.

Tetrathiomolybdate (TM) was first discovered when cattle and sheep grazing on certain pastures in New Zealand or Australia developed a severe neurological disease, called swayback, later identified as being due to severe copper deficiency [38-40]. It was found that the pastures had high molybdenum content in the soil and grass, and that in the sulfur rich rumen of the animals, molybdenum was converted to thiomolybdates [41,42]. Later, from work on rats, it was found that the one containing four sulfurs, tetrathiomolybdate, now known as TM, had the most anticopper potency [43,44]. TM does not directly bind copper, so it is not a copper chelator. It forms a three way complex with copper and protein which is quite stable [43-46]. Thus it is a "complexor", rather than a chelator of copper. TM has seen

significant veterinary use for the treatment of acute copper poisoning in sheep, where it has proven to be life saving [46].

In WD, there is a therapeutic dilemma in a patient who present with acute neurologic symptoms. Penicillamine [13-15] and trientine [17] both causes neurologic worsening in a high percentage of these patients and much of this increased damage is permanent. So, in our opinion, the use of these drugs in these patients is contraindicated. Further, zinc is too slow acting to be optimal in these patients. While zinc does not catalyze neurologic worsening, it takes 6-12 months to control further copper toxicity, and the disease can slowly progress as a result of its own natural history during this period.

Into this therapeutic hiatus, the Brewer group introduced TM. TM is used, along with zinc, in a dose of 120 mg/day, in 6 divided doses, 20 mg 3 times daily with meals, and 20 mg 3 times daily between meals, for 8 weeks [47]. This approach has two mechanisms of action for TM. TM given with food complexes food copper with food protein. This complex is not absorbed and puts the patient into an immediate negative copper balance. TM given away from food is well absorbed and forms the tripartite complex with serum free copper and albumin. Once complexed the free copper is no longer available for toxicity. This complex builds up in the blood and reaches a plateau at about 2 weeks, as metabolism by the liver equates with formation. By about 2 weeks, further copper toxicity is halted.

Using this protocol a 55 patient open label study was done in patients presenting with acute neurologic symptoms [48]. To evaluate efficacy, an instrument was developed called the Semi-Quantative Neurological Exam (SQNE) which was used by collaborating neurologists to evaluate disease stability or worsening. Using this criterion, 2 out of the 55 patients (3.6%) worsened. It was concluded that an occasional patient will worsen because of the natural history of the disease, regardless of what treatment is used. But this low percentage is vastly better than the estimated 50% of neurologic worsening with penicillamine [13], and 26% worsening with trientine [17].

Since trientine had never been evaluated for treating the acute neurologic presentation, a double blind comparison was done of trientine, 1.0 g daily in two divided doses, with TM, 120 mg daily in six divided doses, for 8 weeks. Patients presenting with acute neurologic WD were randomized into the two groups. The SQNE instrument was used at baseline, then at weekly intervals for the 8 weeks. According to the SQNE, 6 of 23 (26%) of trientine treated patients worsened neurologically, and only 1 of 25 (4%) of TM treated patients worsened, statistically significant at p=0.05 [17]. Further, the trientine treated patients who worsened mostly did not do well, 3 of them dying, and 2 others not showing much recovery.

When the serum free copper levels during the study were examined, it was found that TM controlled (reduced) free copper levels early, and kept these levels near zero [49]. Trientine did not reduce the free copper levels, and in fact, there was a pronounced spike (elevation) in free copper temporally related with neurologic worsening in several of the patients who worsened [49].

There were two side effects with TM therapy (Table 1). One was bone marrow suppression with anemia and occasionally leucopenia. This occurred in 10-15% of patients after about 4-6 weeks of treatment [17]. It is due to bone marrow depletion of copper since proliferation of bone marrow cells requires copper, and TM is a very potent agent in lowering copper availability. It is quickly responsive to a drug holiday of a few doses, followed by a dose reduction by one half, or one can

avoid the problem by simply reducing the dose by a half in the first place. The second side effect also occurs in about 10-15% of cases. It is a further elevation of AST and ALT levels, usually to three to four times the upper limit of normal, again at about 4-6 weeks after initiation of therapy [17]. Since this has not been seen in several hundred cancer patients treated with TM, and since in a clinical trial in primary biliary cirrhosis [50], TM actually lowered AST and ALT levels, it is clear that this side effect is specific to WD, no doubt due to the large load of hepatic copper these patients have. In the primary biliary cirrhosis double blind trial, 13 patients were given TM in sufficient dose to lower the serum Cp to 10-15 mg/dl, about half normal, and 15 patients were given placebo, for 13 months. Primary endpoints of reduction in ALT and AST levels, and tumor necrosis factor alpha, were achieved. Adverse events in TM patients were limited to mild anemia and leucopenia if the Cp was pushed too low, with quick recovery by lowering the TM dose. These results show that TM does not raise AST or ALT in non-Wilson's patients. TM is the only anticopper drug that can remove copper from metallothionein, and since much of the hepatic copper in WD is bound to metallothionein, it appears these transaminase elevations are due to shifting copper pools in the WD liver caused by TM. This results in a mild increase in hepatitis. This is also responsive to a brief drug holiday, or lowering the TM dose, and is always transitory.

Since both side effects do not occur early in TM therapy and both are responsive to halving the dose, a drug regimen of a full loading dose of TM for two weeks, then lowering the dose by half for the next 14 weeks was tried. Thus, with this regimen the patient receives the full total dose of TM, or a little more. This regimen markedly reduced the incidence of both of these side effects [Brewer, unpublished].

In these studies a therapeutic dose of zinc, 50 mg 3 times per day has been given with the TM regimen. The reason is that zinc induces hepatic methallothionein which will bind up some free copper in the liver and reduce liver damage. It also makes a smooth transition to zinc maintenance therapy. Patients are treated with zinc indefinitely. They recover neurologic function very nicely, mostly in the first year, but some in the second year as well [17,48]. Depending on the severity of the brain damage when therapy is started, some disability may persist.

Treatment of Various Phases of Wilson's Disease

For several decades, after the diagnosis of WD, treatment was simple- just push the penicillamine button. And unfortunately, some uninformed physicians still do that. But the modern treatment of WD has evolved, and outcomes are much better if different phases of the disease are considered, and appropriate treatment used for each. Treatment of the various phases will be considered next. Table 2 summarizes treatment recommendations for each phase.

Phase of Patient	Treatment Choice	
	First	Second
Hepatic failure presentation	Trientine and zinc (4-6 months)	Penicillamine and zinc (4-6 months)
Neurologic presentation	Tetrathiomolybdate (if available)	Zinc
Maintenance	Zinc	Trientine
Presymptomatic	Zinc	Trientine

Pregnancy	Zinc (loosen copper control)	Trientine (loosen copper control)
Pediatric	Zinc (reduced dose)	Trientine (reduced dose)

Table 2: Recommended anticopper therapy for different phases of Wilson's disease patients.

Treatment of Acute Hepatic Presentation with Elements of Liver Failure

For clarification, here patients presenting with some elements of hepatic decompensation, such as elevated bilirubin level, or reduced albumin level, are considered. Patients only manifesting hepatitis, such as elevated AST and/or ALT levels, are considered presymptomatic, and their treatment is discussed in that section.

The first thing that should be done is evaluate the level of hepatic failure. The prognostic index of Nazer et al. [51] is invaluable for this purpose. This index uses the level of bilirubin, AST, and increase in prothrombin time to develop a score. We should point out that the Nazer et al scoring system has been updated by adding white blood count and albumin to the scoring system. The new system is called the King College Score [52], and it is recommended by the European Association for the Study of Liver (EASL). Since our experience is with the Nazer scoring system, we will use it. The Nazer et al [51] scoring system is reproduced in Table 3. One note of caution- if the patient is hemolyzing, as some patients with the hepatic presentation do, the bilirubin level is no longer useful to evaluate liver function, and this scoring system should not be used. As originally proposed, a score of 1-6 indicated medical treatment would be successful, but a score of 7-12 indicated the patient would die unless a liver transplant was done.

Laboratory measurement	Normal value	Score (in points)				
		0	1	2	3	4
Serum bilirubin	0.2-1.2 mg/dl	<5.8	5.8-8.8	8.8-11.7	11.7-17.5	>17.5
Serum aspartate transaminase (AST)	10-35 IU/L	<100	100-150	151-200	201-300	>300
Prolongation of prothrombin time (seconds)	0	<4	04-Aug	09-Dec	13-20	>20

Table 3: Prognostic Index of Nazer et al. [51].

The index was developed when the only medical treatment was penicillamine. All patients with a score of 7 or above died in spite of penicillamine treatment. A treatment regimen where the index can be pushed up to 9 for medical treatment has been developed using a combination of trientine and zinc, both in their standard therapeutic doses, but doses separated from each other by at least one hour (Table 2). This is maintained for 4-6 months, then one is stopped and the other continued for maintenance therapy. Using this regimen, patients with Nazer scores as high as 9 have been successfully treated [53]. One caution - patients with Nazer scores of 7-9 have marginal hepatic function. If during medical therapy, liver function begins deteriorating, hepatic transplantation may be necessary to save the patient's life.

This regimen may be more effective than penicillamine alone due to the addition of zinc. Zinc will induce hepatic metallothionein, which will bind up some of the hepatic copper, and in that way help reduce further hepatic copper toxicity. Penicillamine can be substituted for trientine in this regimen (Table 2) but that is a second choice, because of the lower toxicity of trientine (Table 1).

Treatment of the Acute Neurologic Presentation

Many of the rationales for the recommendations for treating this phase of WD is given in the sections dealing with the individual anticopper drugs. Thus, penicillamine and trientine often make this type of patients neurologically worse (originally estimated at 50% for penicillamine [13] recently measured at 30% for penicillamine [15], and measured at 26% for trientine [17], and patients who worsen, often do not recover. Thus, these two drugs are contraindicated in treating this kind of patient. It has been suggested that this worsening induced by chelators can be avoided by starting with low dose of drug and gradually escalating the dose. However, there is no published data that this approach works, and those physicians who have reported to the author on their experience with this approach, have said it doesn't work. So, at this time, the recommendation is not to use chelators for initial neurological therapy. Zinc, while it doesn't have the effect of drug catalyzed worsening that the other two drugs have, is slow acting, and the disease can progress as a result of its own natural history during the 6-12 months it takes zinc to gain control of further copper toxicity.

Thus, TM is the first choice for treating this kind patient (Table 2). If TM is unavailable, zinc is the second choice. The use of either trientine or penicillamine is not recommended for this type of patient because too many disastrous outcomes from use of these drugs have been seen.

Maintenance Therapy

Maintenance therapy is defined as the lifelong therapy after adequate initial treatment of the hepatic or neurologic presentation, or in the case of presymptomatic patients, from time of diagnosis. The first choice for maintenance therapy is zinc (Table 2). Trientine is a reasonable second choice but zinc is chosen as first because of its fewer side effects. Some side effects initially assigned to zinc, inhibition of lymphocytic function [34], causing pancreatitis [26], and a negative effect on cholesterol levels [30] were just not true, as has been shown. Zinc does cause gastric intolerance in 5-10% of patients (Table 1). This can often mitigated by taking the first morning dose midmorning instead of prior to breakfast, or taking offending doses with a little protein (lunch meat, hamburger meat, jello, cheese - no bread). If the irritation cannot be adequately mitigated, trientine should be taken. This is a much better choice than becoming only partially compliant, or non-compliant, with prescribed zinc therapy.

It has been published (reference [54] is an example) that a larger number of zinc treated WD patients do not do as well long term as chelator treated patients. Another example of a somewhat negative

report on zinc therapy is a paper where 17 symptomatic WD patients were treated with zinc from the beginning. They found that some liver disease patients suffered deterioration in liver function. Two of 10 patients with neurologic disease developed new hepatic disease [55]. Then there is the paper by Gunther et al. [56]. These authors found that 36 of 84 (43%) patients were not adequately treated with zinc, using an oral 64 Cu absorption test. But the problem with the papers is that these authors have not verified compliance status in their long-treated patients. It has been shown in 40 out of 40 patients, in which nurses were administering the zinc, zinc was fully effective as measured by copper balance and 64 Cu absorption test [29]. No drug will work if it is not taken adequately. Compliance is a problem for all drug treatments of WD, because it is a lifelong therapy and many of the patients are young. However, it is more of a problem for zinc therapy because of the gastric irritation caused by zinc in some of the patients. This becomes a partial barrier to taking all the doses of the drug, and an encouragement to take it with food, which renders it much less effective.

In a large series of carefully followed patients, where 24 hour urine samples were frequently sent in by mail to check compliance, intermittent compliance problems occurred in about 25% of patients [35]. These patients were counseled and all resumed adequate therapy. Only one patient whose liver disease progressed on zinc therapy was observed. While his urine zinc levels seemed to indicate he was taking his zinc, his urine copper levels gradually increased. After he died of progressive liver failure, his wife sent back multiple bottles of the zinc that had been provided him free. He was taking zinc only a week or two before his urine test, but not otherwise. His wife said the zinc bothered his stomach.

Based on these long term studies, zinc is clearly effective for maintenance therapy in all cases of WD, if a patient takes it. Trientine is a good second choice. Penicillamine should not be used for long term therapy because of its long term side effects, some of which are not manifested until several years of therapy.

Treatment of the Presymptomatic Patient

These patients are usually identified as the result of family workups. They are usually siblings of an affected patient. Once diagnosed, it is important to treat them, because the disease is close to 100 % penetrant, and they will surely become ill with either liver disease or brain disease if untreated. So it is good preventive medicine to diagnose and then treat these patients. These type of patients will quite often have evidence of some hepatitis, as revealed by elevated AST and ALT levels. These patients with laboratory evidence of hepatitis are viewed as still presymptomatic, and are treated as such. If the patient has evidence of hepatic decompensation, such as elevated bilirubin or low albumin, they are treated as an hepatic presentation, as discussed in that section.

The first choice for treating presymptomatic patients is zinc (Table 2). As discussed in the zinc section, it has few side effects and it is the easiest to monitor. It has 100% efficacy, if compliance isn't a problem [57].

The second choice is trientine (Table 2). Trientine is particularly a good choice for patients who have enough gastric intolerance of zinc that it threatens compliance. Although trientine has more side effects, it is much better to be on trientine and risk those side effects than to be on zinc and comply so poorly that the disease becomes increasingly symptomatic.

Treatment of the Pregnant Patient

There is no restriction against pregnancy in WD patients as long as they are in the maintenance phase of therapy, and as long as hepatic function is deemed adequate by the obstetrician. It is extremely important to maintain anticopper therapy during pregnancy to protect the health of the mother. During the period when penicillamine was the only therapy, and knowing that penicillamine is teratogenic, some pregnant women stopped penicillamine, with disastrous results, including many deaths [3,6].

The first choice for treatment during pregnancy is zinc (Table 2). The Brewer group had good results with zinc therapy during pregnancy, treating 26 pregnancies in 19 women, with good protection of the mother's health, and with only two birth defects [37]. Interestingly, both of these birth defects were in women who had the tightest control of copper, with quite low 24 hour urine copper values. This suggests that birth defects may be at a greater risk if the copper availability to the fetus is low. Copper deficiency is a known teratogenic entity. These observations have led to a recommendation to loosen up on copper control during pregnancy (Table 2). Normally during zinc therapy it is recommended that the 24 hour urine copper be kept between 60 and 125 µg (normal is 50 µg or below, but WD patients remain higher for years with the slow release of stored hepatic copper). During pregnancy, the 24 hour urine copper should be kept between 75 and 150 µg, a little higher than usual, to try to be sure to provide the fetus with adequate copper.

The second choice for treating the pregnant patient is trientine (Table 2). There are scattered reports of pregnant patients treated successfully with trientine. Based on experience with zinc, recommendations are against tight control of copper with trientine during pregnancy, but it is a little more difficult to make a specific recommendation, since 24 hour urine copper is not a direct reflection of body copper loading, as it is with zinc. Treating pregnant patients with penicillamine is not recommended because of its teratogenicity.

Treatment of the Pediatric Patient

If a pediatric patient presents clinically with hepatic or neurologic symptoms, they should be treated as given in those clinical sections. For maintenance therapy, zinc is recommended as first choice (Table 2) with a reduced dose depending on age and/or weight. For patients up to age 6, the dose is 25 mg 2 times/day. For ages 6-15, or with a weight less than 125 pounds, the dose is 25 mg 3 times/day, after age 15, or a weight of 125 pounds, the adult dose of 50 mg 3 times/day is used.

These doses have been successfully used in 34 pediatric patients [36]. These same doses have subsequently been successfully used in a pediatric study by Marcellini et al. [58]. This latter study had many children in younger age groups, while the first study [36] was a bit thin with very young children. These two studies demonstrate congruently that zinc is an excellent choice for treating pediatric patients. The Marcellini et al. [58] study also showed with repeat liver biopsy that the liver damage, which is present in all these children, gradually improves over years of zinc therapy.

The second choice for treating this group would be trientine (Table 2), although there is limited experience with appropriate dosing.

Conclusion

There are two major problems with the current treatment of WD. One is, in the absence of TM availability, too many physicians are treating neurologically presenting patients with a chelator, penicillamine or trientine. This is a disastrous mistake, because large numbers of these patients are permanently disabled. Until TM is available, and this is being worked on, zinc is a far better choice for these patients. Patients may worsen a little before zinc gains control of copper toxicity, but the disastrous drug-catalyzed worsening is avoided. The approval of TM for neurologically presenting patients is sorely needed to fill this therapeutic hiatus.

The second problem is that some authors are inappropriately claiming "zinc failures" during maintenance therapy: It must be understood that zinc is 100% effective if taken properly. Reports to the contrary are from authors who have not evaluated compliance, and noncompliance due to gastric irritation is usually the reason that zinc is thought to be ineffective.

A new zinc formulation solving the problem of gastric irritation would be very useful to a large number of WD patients, and one is in the works [59].

Zinc is available, it is usually cheap, it is effective, and in most patients well-tolerated, so it is appropriately becoming a mainstay of WD therapy. Zinc can also be relatively expensive, if taken as Galzin, the prescription drug. But many patients take over the counter forms of zinc which are inexpensive. A common salt used is zinc gluconate, which like the zinc salt in Galzin, zinc acetate, is much better tolerated than zinc sulfate, and more effective than zinc oxide.

References

1. Brewer GJ (2000) Recognition, diagnosis, and management of Wilson's disease. Proc Soc Exp Biol Med 223: 39-46.

2. Schilsky ML (1996) Wilson disease: genetic basis of copper toxicity and natural history. Semin Liver Dis 16: 83-95.

3. Scheinberg IH Sternlieb I (1984) Wilson's Disease. In: Smith LHJ (ed) Major Problems in Internal Medicine, WB Saunders Company, Philadelphia, USA.

4. Brewer GJ (2001) Wilson's Disease: A Clinician's Guide to Recognition, Diagnosis, and Management, Kluwer Academic Publishers, Boston.

5. Brewer GJ (2015) Wilson Disease. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J (eds) Harrison's Principles of Internal Medicine. 19th. Graw-Hill Companies, Inc., New York, pp. 2519-2521.

6. Brewer GJ, Yuzbasiyan-Gurkan V (1992) Wilson disease. Medicine (Baltimore) 71: 139-164.

7. Brewer GJ (2010) Zinc and tetrathiomolybdate for the treatment of Wilson's disease. In Small Molecule Therapy for Genetic Disease, Thoene JF (ed) Cambridge University Press, New York.

8. Bull PC, Thomas GR, Rommens JM, Forbes JR, Cox DW (1993) The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet 5: 327-337.

9. Tanzi RE, Petrukhin K, Chernov I, Pellequer JL, Wasco W, et al. (1993) The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet 5: 344-350.

10. Yamaguchi Y, Heiny ME, Gitlin JD (1993) Isolation and characterization of a human liver cDNA as a candidate gene for Wilson disease. Biochem Biophys Res Commun 197: 271-277.

11. Ala A, Borjigin J, Rochwarger A, Schilsky M (2005) Wilson disease in septuagenarian siblings: Raising the bar for diagnosis. Hepatology 41: 668-670.

12. Walshe JM (1956) Penicillamine, a new oral therapy for Wilson's disease. Am J Med 21: 487-495.

13. Brewer GJ, Terry CA, Aisen AM, Hill GM (1987) Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. Arch Neurol 44: 490-493.

14. Walshe JM, Yealland M (1993) Chelation treatment of neurological Wilson's disease. Q J Med 86: 197-204.

15. Kalita J, Kumar V, Chandra S, Kumar B, Misra UK (2014) Worsening of Wilson disease following penicillamine therapy. Eur Neurol 71: 126-131.

16. Walshe JM (1982) Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. Lancet 1: 643-647.

17. Brewer GJ, Askari F, Lorincz MT, Carlson M, Schilsky M, et al. (2006) Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. Arch Neurol 63: 521-527.

18. Schouwink G (1961) De hepatocecerbrate degeneratie, met een onderzoek naar de zonkstofwisseling. MD thesis (with summary in English, French, and German). University of Amsterdam.

19. Hoogenraad TU, Van den Hamer CJ, Van Hattum J (1984) Effective treatment of Wilson's disease with oral zinc sulphate: two case reports. Br Med J (Clin Res Ed) 289: 273-276.

20. Hoogenraad TU, Van Hattum J, Van den Hamer CJ (1987) Management of Wilson's disease with zinc sulphate. Experience in a series of 27 patients. J Neurol Sci 77: 137-146.

21. Brewer GJ, Hill GM, Prasad AS, Cossack ZT, Rabbani P (1983) Oral zinc therapy for Wilson's disease. Ann Intern Med 99: 314-319.

22. Hill GM, Brewer GJ, Prasad AS, Hydrick CR, Hartmann DE (1987) Treatment of Wilson's disease with zinc. I. Oral zinc therapy regimens. Hepatology 7: 522-528.

23. Hill GM, Brewer GJ, Juni JE, Prasad AS, Dick RD (1986) Treatment of Wilson's disease with zinc. II. Validation of oral 64copper with copper balance. Am J Med Sci 292: 344-349.

24. Brewer GJ, Hill GM, Dick RD, Nostrant TT, Sams JS, et al. (1987) Treatment of Wilson's disease with zinc: III. Prevention of reaccumulation of hepatic copper. J Lab Clin Med 109: 526-531.

25. Brewer GJ, Hill G, Prasad A, Dick R (1987) The treatment of Wilson's disease with zinc. IV. Efficacy monitoring using urine and plasma copper. Proc Soc Exp Biol Med 184: 446-455.

26. Yuzbasiyan-Gurkan V, Brewer GJ, Abrams GD, Main B, Giacherio D (1989) Treatment of Wilson's disease with zinc. V. Changes in serum levels of lipase, amylase, and alkaline phosphatase in patients with Wilson's disease. J Lab Clin Med 114: 520-526.

27. Brewer GJ, Yuzbasiyan-Gurkan V, Lee DY, Appelman H (1989) Treatment of Wilson's disease with zinc. VI. Initial treatment studies. J Lab Clin Med 114: 633-638.

28. Lee DY, Brewer GJ, Wang YX (1989) Treatment of Wilson's disease with zinc. VII. Protection of the liver from copper toxicity by zinc-induced metallothionein in a rat model. J Lab Clin Med 114: 639-645.

29. Brewer GJ, Yuzbasiyan-Gurkan V, Dick R, (1990) Zinc therapy of Wilson's disease: VIII. Dose response studies. J Trace Elem Exp Med 3: 227-234.

30. Brewer GJ, Yuzbasiyan-Gurkan V, Johnson V (1991) Treatment of Wilson's disease with zinc. IX: Response of serum lipids. J Lab Clin Med 118: 466-470.

31. Yuzbasiyan-Gurkan V, Grider A, Nostrant T, Cousins RJ, Brewer GJ (1992) Treatment of Wilson's disease with zinc: X. Intestinal metallothionein induction. J Lab Clin Med 120: 380-386.

32. Brewer GJ, Yuzbasiyan-Gurkan V, Johnson V, Dick RD, Wang Y (1993) Treatment of Wilson's disease with zinc: XI. Interaction with other anticopper agents. J Am Coll Nutr 12: 26-30.

33. Brewer GJ, Yuzbasiyan-Gurkan V, Johnson V, Dick RD, Wang Y (1993) Treatment of Wilson's disease with zinc XII: dose regimen requirements. Am J Med Sci 305: 199-202.

34. Brewer GJ, Johnson V, Kaplan J (1997) Treatment of Wilson's disease with zinc: XIV. Studies of the effect of zinc on lymphocyte function. J Lab Clin Med 129: 649-652.

35. Brewer GJ, Dick RD, Johnson VD, Brunberg JA, Kluin KJ, et al. (1998) Treatment of Wilson's disease with zinc: XV long-term follow-up studies. J Lab Clin Med 132: 264-278.

36. Brewer GJ, Dick RD, Johnson VD, Fink JK, Kluin KJ, et al. (2001) Treatment of Wilson's disease with zinc XVI: treatment during the pediatric years. J Lab Clin Med 137: 191-198.

37. Brewer GJ, Johnson VD, Dick RD, Hedera P, Fink JK, et al. (2000) Treatment of Wilson's disease with zinc. XVII: treatment during pregnancy. Hepatology 31: 364-370.

38. Ferguson WS, Lewis AL, Waterson SJ (1943) The teart pastures of Somerset, I: the cause and cure of teartness. J Agri Sci 33:44.

39. Dick AT, Bull LB (1945) Some preliminary observations on the effect of molybdenum on copper metabolism in herbivorous animals. Aust Vet J 21: 70-72.

40. Miller RF, Engel RW (1960) Interrelations of copper, molybdenum and sulfate sulfur in nutrition. Fed Proc 19: 666-671.

41. Dick AT, Dewey DW, Gawthorne JM (1975) Thiomolybdates and copper-molybdenum-sulfur interaction in ruminant nutrition. J Agri Sci 85: 567-568

42. Mason J (1990) The biochemical pathogenesis of molybdenum-induced copper deficiency syndromes in ruminants: towards the final chapter.Ir Vet J 43:18-21.

43. Mills CF, El-Gallad TT, Bremner I (1981) Effects of molybdate, sulfide, and tetrathiomolybdate on copper metabolism in rats. J Inorg Biochem 14: 189-207.

44. MIlls CF, El-Gallad TT, Bremner I, Weham G (1981) Copper and molybdenum absorption by rats given ammonium tetrathiomolybdate. J Inorg Biochem 14: 163-175.

45. Bremner I, Mills CF, Young BW (1982) Copper metabolism in rats given di- or trithiomolybdates. J Inorg Biochem 16: 109-119.

46. Gooneratne SR, Howell JM, Gawthorne JM (1981) An investigation of the effects of intravenous administration of thiomolybdate on copper metabolism in chronic Cu-poisoned sheep. Br J Nutr 46: 469-480.

47. Brewer GJ, Dick RD, Yuzbasiyan-Gurkin V, Tankanow R, Young AB, et al. (1991) Initial therapy of patients with Wilson's disease with tetrathiomolybdate. Arch Neurol 48: 42-47.

48. Brewer GJ, Hedera P, Kluin KJ, Carlson M, Askari F, et al. (2003) Treatment of Wilson disease with ammonium tetrathiomolybdate: III. Initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. Arch Neurol 60: 379-385.

49. Brewer GJ, Askari F, Dick RB, Sitterly J, Fink JK, et al. (2009) Treatment of Wilson's disease with tetrathiomolybdate: V. Control of free copper by tetrathiomolybdate and a comparison with trientine. Transl Res 154: 70-77.

50. Askari F, Innis D, Dick RB, Hou G, Marrero J, et al. (2010) Treatment of primary biliary cirrhosis with tetrathiomolybdate: results of a double-blind trial. Transl Res 155: 123-130.

51. Nazer H, Ede RJ, Mowat AP, Williams R (1986) Wilson's disease: clinical presentation and use of prognostic index. Gut 27: 1377-1381.

52. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, et al. (2005) Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. Liver Transpl 11: 441-448.

53. Askari FK, Greenson J, Dick RD, Johnson VD, Brewer GJ (2003) Treatment of Wilson's disease with zinc. XVIII. Initial treatment of the hepatic decompensation presentation with trientine and zinc. J Lab Clin Med 142: 385-390.

54. Weiss KH, Gotthardt DN, Klemm D, Merle U, Ferenci-Foerster D, et al. (2011) Zinc monotherapy is not as effective as chelating agents in treatment of Wilson disease. Gastroenterology 140: 1189-1198.

55. Linn FH, Houwen RH, van Hattum J, van der Kleij S, van Erpecum KJ (2009) Long-term exclusive zinc monotherapy in symptomatic Wilson disease: experience in 17 patients. Hepatology 50: 1442-1452.

56. Gunther P, Kuhn H.J, Herman W, (2013) Monitoring therapy in Wilson's disease by the oral radiocopper test. Aktuelle Neurologie 40: 195-199.

57. Brewer GJ, Dick RD, Yuzbasiyan-Gurkan V, Johnson V, Wang Y (1994) Treatment of Wilson's disease with zinc. XIII: Therapy with zinc in presymptomatic patients from the time of diagnosis. J Lab Clin Med 123: 849-858.

58. Marcellini M, Di Ciommo V, Callea F, Devito R, Comparcola D, et al. (2005) Treatment of Wilson's disease with zinc from the time of diagnosis in pediatric patients: a single-hospital, 10-year follow-up study. J Lab Clin Med 145: 139-143.

59. Brewer GJ (2012) Copper excess, zinc deficiency, and cognition loss in Alzheimer's disease. Biofactors 38: 107-113.