Review Article

Clinical management of Wilson disease

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Abstract: The availability of effective therapies distinguishes Wilson disease (WD) from other inherited neurometabolic diseases. The cause of hepatic, neurologic or psychiatric symptoms is copper overload and subsequent copper toxicity. Diagnosed WD patients require life-long pharmacologic therapy that is focused on reversal of copper overload with maintenance of a long-term negative copper balance. This is associated with the rapid control of free or non-ceruloplasmin bound copper that is mostly responsible for acute cytotoxic effects. Currently available therapies can be divided into chelators and zinc salts. They have different mechanisms of action and the onset of efficacy that influences their selection in acute and chronic stages of therapy. We review the use of D-penicillamine and trientine for chelation therapies, including the required monitoring of therapy for its efficacy and possible overtreatment with iatrogenic copper deficiency. Additionally, the use of zinc salts is also discussed, including a possibility of its use for the initial therapy in an acute stage of the disease. Supportive and symptomatic therapies for liver failure and neuropsychiatric symptoms are also reviewed.

Keywords: Wilson disease (WD); copper; ATP7B; chelation; zinc; D-penicillamine; trientine; liver transplantation

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Wilson disease (WD) is an inherited metabolic disorder of impaired copper transport caused by biallelic mutations in the *ATP7B* gene (1,2). A loss of function of this copper transporter results in a chronic copper accumulation in the liver and subsequently in the central nervous system (3). Excessive free (non-ceruloplasmin bound or NCC) copper triggers cytotoxic effects mostly in hepatic and central nervous tissues, leading to the typical clinical phenotypes with predominantly hepatic, neurologic or psychiatric symptoms (4).

Even though the recent identifications of several patients with an atypical late onset in the 7th and 8th decades of life support the concept that some *ATP7B* mutations have reduced penetrance, in the overwhelming majority of WD cases an untreated copper buildup is associated with devastating and eventually fatal consequences (3-7). Thus, diagnosed WD patients require pharmacologic therapy, even if they are asymptomatic. The initial goal of therapy is to reverse copper overload with increased plasma NCC copper levels and establish a negative copper balance with a rapid control of NCC copper levels (8,9). The next step is a maintenance therapy that continues to control free copper levels without inducing iatrogenic copper deficiency. This phase of pharmacotherapy typically starts after disease symptoms and biochemical abnormalities have improved, and this is typically observed in 2–6 months after initiation of chelation therapy during which NCC copper values are reduced to normal levels. Maintenance therapy is potentially life-long unless liver transplant is performed or future use of gene therapy will be truly a curative therapy (8,9).

Currently available medications to treat WD are chelating agents that non-specifically chelate copper and promote urinary copper excretion, and zinc salts that reduce the absorption of copper from the gastrointestinal tract. Both groups of medications have a different onset of action with chelators immediately binding the circulating NCC or free copper pool. Hepatic copper content remains high in treated WD patients supporting the removal of circulating copper as the primary mechanism of action of chelators (10,11). Moreover, they do not directly bind stored copper

in the brain because available chelators do not cross the blood brain barrier. Copper removal from the central nervous system is achieved by its mobilization and shift to plasma pool where it can be chelated and removed through the urinary excretion (12). Relatively rapid onset of action favors chelating agents to be used in the acute phase of decoppering therapy and they can also be used for a long-term maintenance therapy (8,9).

D-penicillamine has now an established place as the most commonly used chelator in the treatment of WD and its major effect is the promotion of the urinary excretion of copper (13,14). It also binds other metals and additional indications include cystinosis and rheumatoid arthritis (15). It needs to be taken either one hour before meals of two after meals because food reduces its absorption by almost 50% (16). It also should not be taken with antacids or iron supplements. The usual target dose of D-penicillamine during the initial therapy is 1,000–2,000 mg/day (or 900–2,100 mg if 300 mg tablets are used) given in 2–4 divided dosages but starting with incremental doses is recommended to reduce adverse side effects and to reduce a risk of paradoxical worsening in patients with predominantly neurologic symptoms (8,9). The starting dose for patients with neurologic symptoms should be 250–500 mg/day (or 300–600 mg/day) with a careful increment by 250 mg every 5–7 days to monitor patients for a possible worsening and side effects and a typical maximal dose in neurologic patients is 1,500 mg/day (17). D-penicillamine can be also used in children and the dosing in these patients is 20 mg/kg/day and is rounded to the nearest 250 or 300 mg (8).

D-penicillamine has a strong cupreuremic effect and 24-H urine copper assay is used to monitor the therapeutic response (8,9). Chelation therapy should also normalize NCC copper but this test is not generally available and the calculation of NCC based on total plasma copper and ceruloplasmin levels may be imprecise if plasma ceruloplasmin values are at the lower limit of detectability and not fully quantified. The dose is adjusted based on 24-H urine copper assay and excretion of copper may exceed 1,000 µg (16 µmol) per day at the initiation of the therapy. D-penicillamine can be also used for a long-term maintenance therapy and this dose is lower than during acute chelation (8,18). This dosing is usually 750–1,000 mg/day administered in two divided doses with expected daily urine excretion between 200 and 500 µg (3–8 µmol). Urine copper levels below 200 µg (3 µmol)/24 hours suggest overtreatment with iatrogenic copper deficiency or noncompliance with treatment (8,9). Efficacy of chelation therapy can be also assessed by measurement of 24-hour urine copper that is collected 48 hours after temporary cessation of therapy. The copper urine values less than 75 µg per day indicate an adequate copper control.

The transition to a chronic therapy is based on clinical improvement and normalization of liver function tests in hepatic patients (19-21). The typical interval in hepatic patients is after 2–6 months of chelating therapy but the additional clinical and laboratory improvement can be observed up to one year (19-22). Neurologic patients tend to have much slower rate of clinical improvement and recovery and a partial or complete neurologic recovery may be observed up to three after the initiation of chelation therapy (17,23-25).

One of possible drawbacks of D-penicillamine is frequent adverse effects that can be divided into acute and chronic types. Up to one third of patients would eventually stop this therapy and there is a high risk on non-compliance with a possibility of further worsening of neuropsychiatric or hepatic symptoms (8,9,21,25). Early or acute sensitivity reactions include fever, lymphadenopathy, cutaneous eruptions, proteinuria and signs of bone marrow suppression with neutropenia or worsening of thrombocytopenia, which is also a consequence of hypersplenism (26). Slower rate of dose titration or a brief therapy with steroids have been suggested to mitigate these problems but if alternative medication, such as trientine is available, the change of chelating agent may be a more suitable next step in WD therapy (22,27). Chronic adverse effects include nephrotoxicity with proteinuria, a lupus-like reaction with hematuria, proteinuria, and positive antinuclear antibody, progeric changes in the skin, pemphigoid lesions, lichen planus, and aphthous stomatitis, myasthenia gravis-like syndrome, and polymyositis (28-33). D-penicillamine interferes with collagen cross-linking and this may account some dermatologic side effects (34). It will also interfere with wound healing and the therapy needs to be interrupted if surgery is planned. D-penicillamine has also an antipyridoxine effect and supplementation of pyridoxine (vitamin B6) at the daily dose of 25–50 mg daily or monitoring of pyridoxine levels has been recommended (35).

Another significant complication of D-penicillamine chelation therapy is a paradoxical worsening of neurologic symptoms in patients who presented with neuropsychiatric phenotype, typically within the first six months of the therapy (22,25,36-38). This has been observed even after an appropriate therapy is initiated in a timely manner and can be see also in other mediations used to treat acute neurologic symptoms of WD. The presumed

mechanism behind this worsening is a rapid mobilization of unbound copper resulting in higher blood NCC copper and triggering a cytotoxic effect in neuronal tissue with subsequent neurologic deterioration in treated patients (4). Correlation between the stability of NCC control without additional elevations of NCC values and the favorable neurologic outcomes has been reported but again, NCC copper assay is not readily available as a routine clinical test to monitor elevation of NCC copper after the treatment initiation (39,40). Original reports indicated that D-penicillamine therapy has the highest risk of this phenomenon and 20–35% of treated patients with neurologic presentation have experienced further deterioration that is often irreversible (36). A more recent retrospective analysis of WD patients showed no statistical difference between the rate of neurologic complications between D-penicillamine and other medications for WD and it remains unsettled whether there is difference in the risk of neurologic deterioration among different WD medications (22,25). The severity of presenting neurologic symptoms and the extent of structural changes detected by magnetic resonance imaging with early signal changes in the basal ganglia, thalamus and the brainstem are also risk factors for paradoxical worsening (38). Recommenced management of the paradoxical neurologic worsening includes a reduction of the dose of D-penicillamine or even a temporary interruption of chelation if no other treatment options are available (8,9).

Trientine was originally developed as the second line therapy for patients who did not tolerate D-penicillamine (8,9). It is a chelator with a high affinity to copper and the bound copper is also removed through urinary excretion. It has been suggested that trientine has lower cupreuremic effect than D-penicillamine and daily copper excretion in the range of 200–500 µg (3–8 µmoles) are commonly observed in WD patients on trientine who are responding to therapy as judged by clinical improvement (18,41). The target dose of trientine during the initial therapy is 750–1,500 mg/day divided in two or three doses and it also should be taken before food (8,9,42). Similarly to D-penicillamine therapy, trientine should be also started gradually in patients with neurologic symptoms with 250 mg increments every 5–7 days. Trientine has been used successfully in patients with decompensated liver failure. The typical maintenance dose is 750 or 1,000 mg per day and the dose is adjusted based on 24-copper urine values. Daily urinary copper excretion below 200 µg may indicate either nonadherence to therapy or induction of copper deficiency from overtreatment (8,9,42). There is no established weight-based dose in the pediatric population and most of the experts use the dose of 20 mg/kg/day rounded off to the nearest 250 mg with similar dosing frequency as in adults (8).

One of the major advantages of trientine is the quite favorable safety profile and no toxic reactions are observed in treated patients (8,9). A low frequency of lupus like reaction was described in patients on trientine but they were all treated with D-penicillamine before and it is unclear which drug was triggering this side effect (8). Good safety profile was also reported in pregnant patients and no significant teratogenic effects have been observed (43). Overall, the interruption of anticopper drugs during pregnancy is not advisable because it may cause worsening of neurologic symptoms or liver failure (44). However, breastfeeding is not recommended for mothers treated with trientine. Bone marrow suppression with trombocythopenia and leukopenia is rare and it should prompt an evaluation for evolving copper deficiency from the overtreatment (4).

Paradoxical neurologic worsening has been also observed in patients treated with trientine and the reported incidence was 10–15% of patients experiencing further progression of their neurologic symptoms (42). This would potentially favor trientine as the first line chelation therapy for patients with neurologic symptoms based on previous reports of much higher risk in patients treated with D-penicillamine (36). However, more recent retrospective studies from the European Union suggested that D-penicillamine, trientine and zinc salts had very comparable incidence of paradoxical worsening and actually, one study found the least frequent deterioration in patients treated with D-penicillamine with the reported risk of 2% of neurologic decline, which is much lower from the previous observations (22,25). However, the lack of head to head comparisons between these two chelators and the retrospective nature of most of the studies describing the rate of paradoxical worsening makes it difficult to determine whether there is a superior chelator in terms of the risk of paradoxical worsening. Thus, until more conclusive clinical data are available, the selection of the first line chelation therapy for patients with neurologic phenotype of WD needs to be based on additional factors, including personal experience and the availability of chelators in different regions of the world.

Zinc salts are used to induce negative copper balance through the induction metallothioneins in the enterocytes, which block dietary uptake of copper in the gastrointestinal system (45). Metallothioneins are cysteine-rich proteins that bind various metal ions and are normally present in

the intestine, liver and brain. Zinc is one of the most potent inducers of metallothioneins but copper has the highest affinity for irreversible binding to these proteins. The dietary copper bound to metallothionein is sequestered within the intestinal cells and prevented from absorption into the blood (46-48). Negative copper balance is achieved because copper is removed through the stool after the enterocytes are shed in the intestinal lumen as a part of normal cellular turnover.

There are several zinc salts available and only zinc acetate has been approved by the FDA for treatment of WD (49). Zinc should be taken on an empty stomach and gastric irritation with nausea is the most common side effect. The severity of gastric intolerance may be influenced by the type of salt and zinc gluconate can be used to ameliorate side effects (25,50). The typical dose of zinc in form of acetate or gluconate should contain 50 mg elementary zinc three times a day. There is no established pediatric dose and half of dose with 25 mg three-times a day is commonly used in pediatric population (51). Additionally, zinc sulphate can be used and the dosing for this salt varies from 300 to 1,200 mg/day, usually divided into three doses. The response to this therapy is also monitored by 24-hour copper urine assay but given the difference in mechanism of action, the target copper urine values differ from monitoring parameters of chelation therapies (49). Zinc does not promote urinary copper excretion and an effective treatment reduces the overall copper urinary excretion, reflecting the reduction of copper overload. Daily urinary copper excretion of less than 75 µg indicates an adequate control on zinc therapy (49).

The effects of zinc on metallothioneins expression are cumulative and there is a delay of several months until zinc efficacy peaks and negative copper balance is established. That is why the most common use of zinc is a maintenance therapy after chelation induced a negative copper balance (47,49,52). When a patient is crossed over from a chelator to zinc, these two therapies need to overlap for a period of 2–3 months to maximize the effects on metallothioneins. This may be challenging from the scheduling point of view because both medications need to be taken without food and they should be separated by about two hours to avoid reduced absorption. Monotherapy with zinc has been used for both neurologic and hepatic types of WD. However, zinc alone may be less effective than chelators for controlling the liver disease and a careful monitoring of liver function tests is warranted for patients on a maintenance zinc therapy (53). Given its mechanism of action and safety profile zinc may be also very suitable for treatment of WD during the pregnancy (54).

Even though zinc is most commonly used as a second-line medicine after laboratory signs of copper overload have been normalized by chelators, its use as the first-line therapy has also been advocated (55,56). Asymptomatic patients who are diagnosed during the screening of first degree relatives are very suitable for the initial zinc therapy because the delayed efficacy does not represent a high risk for further deterioration of WD (48,52). Another scenario is its use in patients who developed neurologic symptoms and are naïve to any decoppering therapy (55,56). The justification of zinc as the first-line therapy in these patients is a risk of paradoxical worsening that has been observed with chelators. However, some consider a first-line therapy with zinc too slow to effectively control neurologic phenotype of WD (4,48). A study comparing D-penicillamine and zinc sulphate as the initial therapy has been reported and included 60 patients presenting with neuropsychiatric phenotype (25). The observed rate of further neurologic worsening did not differ between these two drugs. This suggests that the paradoxical worsening in treated neurologic WD patients may be caused by two different mechanisms, overtreating and undertreating. An elevation of the NCC copper after chelators were introduced is thought to be responsible for worsening with trientine or D-penicillamine (8,9,39). That is why lowering the dose of an used chelator has been recommended under these circumstances. It is very plausible that observed neurologic deterioration on zinc therapy may be accounted for by a slower reduction of NCC copper due to a delayed response to this therapy (25,57,58). Monitoring of NCC copper may be helpful to guide the changes in the therapy and in well controlled WD patients the levels of 5–15 µg/dL (0.84–2.4 µmol/L) are the target of the therapy; 25 µg/dL (3.94 µmol/L) and higher levels are seen in patients who are at risk to develop paradoxical neurologic worsening (8,9,39). The future routine availability of this assay rather than calculation of NCC copper from total copper and ceruloplasmin values should improve the monitoring of treated WD patients and guide the necessary medical adjustments.

Copper is an ubiquitous micronutrient and a low copper diet has been suggested for treated WD patients, especially during first two or three years after therapy (8,9). However, dietary changes alone are insufficient to treat copper overload in WD. Shellfish, nuts, chocolate, mushrooms, and organ meats, especially liver tend to have very high copper concentration and should be avoided until the

patients achieve negative copper balance. Additional sources of excessive external copper may be cooking copperware or drinking water if copper plumbing is used. Low copper diet is relatively less useful if zinc therapy is used because zinc blocks copper absorption from alimentary intake (47). Well controlled patients may be more liberal with their diet.

WD patients who develop acute liver failure are candidates for transplantation because of very high mortality and liver transplant under these circumstances is a lifesaving procedure (8,9). Model for end-stage liver disease (MELD) score and Nazer scoring system are used in hepatic patients to indicate the need for liver transplant and they were also specified for WD patients (59,60). Patients after the transplant do not need any additional anticopper therapies because liver transplantation also corrects the genetic defect causing WD. This not only restores copper homeostasis in the liver but also extrahepatic copper metabolism in other tissues as well, most notably in the central nervous system. That is why liver transplant has been also suggested in patients with deterioration neurologic symptoms without any signs of liver failure (61-66). However, the role of liver transplantation as a treatment of neurologic deficits remains controversial. Improvement or even a complete resolution after liver transplantation has been reported in some patients with severe and progressive neurologic deficits who did not respond or deteriorated on chelation therapies. These positive neurologic outcomes are not universal and no improvements or further progression have been also observed in some patients who underwent liver transplant for this indication (67,68). At present there is no consensus regarding the role of liver transplant to reverse neurologic deficits.

Patients with neurologic and psychiatric phenotypes often experience considerable disability from residual symptoms and may benefit from additional symptomatic therapy (24,69). Tremor, dystonia, chorea, Parkinsonism and spasticity are most disabling but also potentially treatable neurologic problems (4). There are no specific therapies developed for neurologic symptoms caused by WD and the symptomatic therapeutic approach is similar to the treatments used for other neurologic conditions. Tremor in WD can be occasionally confused with essential tremor (ET) but most patients have either dystonic tremor or rubral wing beating tremor. "Trial and error" algorithm is commonly employed in tremor patients and action and postural tremor can be ameliorated by medications used in ET, including beta-blockers, such as propranolol or metoprolol, primidone, topiramate, pregabalin or benzodiazepines with a longer half-life, such as clonazepam (70,71). Dystonic tremor is more likely to respond to anticholinergic agents, most commonly trihexyphenidyl or focal therapies with botulinum A or B toxins. Rubral tremor, also known as Holmes tremor has features of cerebellar outflow tremor and it is notoriously resistant to pharmacotherapy (4). Functional neurosurgical procedures, including deep brain stimulation targeting the ventral intermediate nucleus of the thalamus or thalamotomy have been successfully used to control medically refractory tremor (72,73).

Symptomatic therapy of dystonia includes chemodennervation using botulinum A or B toxins and they are now commonly used as the first line of therapy (74). However, botulinum toxins may be not practical in widespread dystonic symptoms and pharmacotherapy with anticholinergic compounds (*trihexyphenidyl* or benztropine) or gaba-ergic compounds (benzodiazepines or baclofen) can be beneficial in these patients. Dopaminergic challenge with either levodopa of dopaminergic agonists can be tried in patients with dystonia but the results vary considerably. The same class of medications can be useful in patients with secondary Parkinsonism but again, the results tend to be less favorable than in idiopathic Parkinson's disease (75). Dystonia and Parkinsonism in WD patients are prototypical examples of secondary etiologies caused by structural brain changes and the outcomes of therapy remain unsatisfactory. Functional neurosurgery using DBS can be carefully considered in severely affected patients (72). Dysphagia and dysarthria/anarthria are common sequelae of orofacial dystonia and they are particularly disabling. Dysphagia also increases the risk of aspiration pneumonia and a careful evaluation by speech therapy is warranted. Electrical stimulation for oropharyngeal dystonia has been tried in WD patients but there are no formal studies available. Many patients require percutaneous endoscopic gastrostomy tube to maintain nutritional requirements and to reduce the risk of aspiration. Tube feeding formulas may have a high copper content and a nutritional consultation focused on reducing the amount of alimentary copper may be helpful.

Involuntary hyperkinetic movements, including chorea or athethosis can be also seen in WD patients and the use of neuroleptics should be limited because the exposure to both typical and atypical neuroleptics has been associated with irreversible neurologic worsening (38,72). Vesicular monoamine transporter 2 blockers, such as tetrabenazine are more suitable options for treatment of hyperkinetic

movements in WD.

Patients with active psychiatric symptoms may also require symptomatic therapies and in general, the selection is not influenced by the primary underlying process with one very important exception. Dopamine blocking agents, such as neuroleptics have been implicated as a potential risk factor for further neurologic worsening in treated WD patients. That is why atypical neuroleptics with potentially lower incidence of secondary Parkinsonism, such as quetiapine, olanzapine or clozapine should be used preferably in these patients to reduce a possibility of paradoxical worsening on therapy (38,76).

Currently available medications to remove excessive copper and maintain negative copper balance in asymptomatic or symptomatic WD patients are fraught with many challenges and even timely start of chelation or zinc therapies may be associated with unfavorable clinical outcomes 4, 8, 9). This risk for suboptimal therapeutic response is further magnified if the effective therapies are delayed due to the initial misdiagnosis of WD (23). Novel therapies, including bis-choline tetrathiomolybdate that forms a tripartite complex with copper and albumin and directly reduces copper content in the liver with the elimination of excess copper via biliary excretion, or gene therapy restoring the expression of the *ATP7B* gene are being currently tested (40,77,78). If successful, they may help to address several unmet needs and improve the long-term results of WD therapies and ultimately the quality of life of WD patients.

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Footnote

Conflicts of Interest: The author has served on advisory board for Wilson Therapeutics AB.

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