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Wilson Disease: An Updated Review on the Drug Management and its Neurological Aspects

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KEYWORDS

Wilson's disease (WD), ATP7BProtein, Copper Metabolism, Chronic Liver Disease, Neurological syndrome

ABSTRACT:

Wilson's disease, stemming from a malfunctioning ATP7B protein, disrupts the body's ability to manage copper effectively. Its clinical impact can range from an inconspicuous condition with no apparent symptoms to severe liver problems, such as acute hepatic failure or long-term liver damage, sometimes accompanied by cirrhosis. Additionally, Wilson's disease can manifest in various neurological and psychiatric symptoms. To prevent overlooking cases of Wilson's disease (WD), especially in patients with subtle symptoms like slight increases in transaminase levels or limited neuropsychiatric issues, it's essential to maintain a vigilant and cautious approach. This proactive approach is crucial to managing and mitigating the impact of the disease on affected families. Recent times have seen the emergence of novel molecular information regarding WD development and metabolic fingerprints of WD abnormalities. Studies on WD patients and animal models have shown that extrahepatic tissues and non-parenchymal liver cells contribute to the liver phenotype and have identified nuclear receptor (NR) dysregulation, epigenetic modifications, and mitochondrial dysfunction as key features of the disease's pathogenesis. This review examines emerging strategies for bettering WD diagnosis and treatment while also outlining current developments in the definition of WD pathophysiology under treatment options for Wilson's disease typically involving the use of chelating agents such as D-penicillamine and trientine. In addition, zinc salts serve as inducers of metallothionein, a protein that helps maintain a healthier copper balance by reducing the levels of free copper in the bloodstream

1. Introduction

Wilson's disease, abbreviated as WD and initially pinpointed by Kinnear Wilson in 1912, is a genetic disorder inherited through an autosomal recessive pattern. Its onset is sporadic and results from mutations occurring in the region of chromosome 13q14 responsible for encoding the ATP7B protein [1] In individuals with homozygous or, more commonly, compound heterozygous mutations, the typical process of copper excretion into bile is disrupted. This disruption occurs due to a deficiency in incorporating copper into apo-ceruloplasmin, which, in turn, hinders the production of holoceruloplasmin. This condition leads to impaired copper metabolism, resulting in copper intoxication as a notable side effect. While the gene responsible for encoding this protein is still intact on chromosome 3, there is an abnormally low level of circulating apo ceruloplasmin (also referred to as ceruloplasmin). Notably, apoceruloplasmin has a shorter half-life compared to holoceruloplasmin. This protein plays a pivotal role as one of the most essential clinical diagnostic markers for Wilson's Disease (WD) The toxicity caused by copper overload, with free copper being the primary agent, operates through two principal mechanisms: Copper overload exerts its toxic effects through two primary mechanisms. Firstly, it induces direct oxidative stress, resulting in lipid peroxidation of cell membranes, DNA, and mitochondria. Secondly, it triggers unregulated apoptosis, causing cell death due to copper-induced alterations in the anti-apoptotic protein

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known as the X-linked inhibitor of apoptosis. This disruption leads to the loss of its inhibitory control over caspase-3 [3]. Current understanding indicates that copper intoxication arises from free copper in the bloodstream rather than copper buildup, which is detrimental to the body. In this context, it's the unbound, free copper that poses a health risk. In recent years, there has been a notable shift in the approach to addressing copper–related health concerns. The conventional method of targeting the removal of copper storage as the primary treatment objective has given way to a more

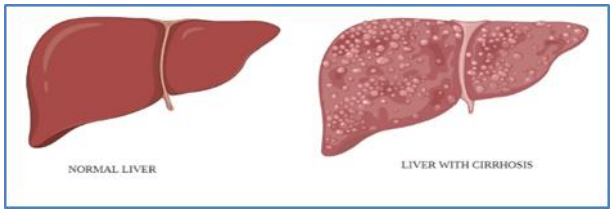

Fig.1. Comparison between normal liver and liver with cirrhosis

contemporary perspective that of normalizing free copper concentration in the bloodstream. This transition represents a pivotal re-evaluation of our approach to managing copper health issues [4,5].

Wilson Disease affects the liver's ability to properly release copper into bile. As the copper accumulates in the liver, the organ starts to suffer harm. When the liver has sustained enough damage, copper is immediately released into the circulation, where it is transported throughout the body.

Fig. 2. Comparison between normal eye and kayser-flesher ring

The Kayser-Fleischer ring, a distinctive feature observed in many individuals with Wilson disease, encircles the pigmented area of the eye. This ring is composed of copper deposits that accumulate in the cornea, specifically on the front surface of the eye another potential manifestation of Wilson disease includes abnormalities in eye movements, which can manifest as a restricted ability to gaze upward this impairment in upward gaza is a noteworthy symptom often observed in individuals with this condition.

2) Epidemiology

Wilson disease (WD) is a rare medical condition with a relatively low prevalence in the global population. Its gene frequency, which represents the occurrence of the gene associated with WD, stands at approximately 0.56%. In practical trems, this means that this gene is found in about 0.56% of the population. Despite this, the illness is far less prevalent in some regions and nations, with particular mutations being reported more commonly in particular groups. Since more than 500 mutations have been discovered to date, the reduced penetrance of mutations is likely reflected by the lower number of real clinically evident instances compared to the population's frequency of allele carriers. In Europe and North America, when considering the genetic mutations associated with Wilson disease, several mutations stand out as the most prevalent. These mutations are noteworthy for their relatively higher occurrence in individuals with the condition. Among these prevalent mutations, four specific ones are frequently encountered:

1. His1069Glu (H1069Q)
2. Arg778Leu (H1069Q)
3. 2007del7 (H1069Q)
4. Met645Arg (H1069Q)

These genetic mutations are significant because they play a key role in the development and manifestation of Wilson disease in affected individuals within these regions. Understanding the prevalence of these mutations is crucial for healthcare professionals in the diagnosis and management of the condition, as it allows for targeted genetic testing and a more accurate assessment of the risk of Wilson disease in affected populations. The prevalence of Wilson disease varies across different regions, and in some countries, it is more common than in others. In particular, Germany, Japan, and Austria have been identified as having some of the highest rates of this condition among their populations. Here are the respective prevalence rates for Wilson disease in these countries.

Countries Name	Rates of Wilson disease in countries
Germany	2.5/100000
Japan	3.3/100000

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Austria	3.0/100000

Table 1: Prevalence rates for Wilson disease

Costa Rica boasts the highest incidence of Wilson disease globally, and this distinctive occurrence may be linked to two important factors: a notably high degree of consanguinity within the population and the possibility of a founder The prevailing mutant form of Wilson disease is Asn 1270 Ser, a genetic variant that was previously predominantly found in specific populations, including those of Sicilian, Lebanese, and Turkish origin [5,6]. This particular mutation once considered relatively rare and geographically restricted, has gained prominence as one of the most frequently observed genetic alterations associated with the disease. Its wider occurrence underscores the complex interplay between genetics and the diverse ancestral backgrounds of individuals affected by Wilson disease Sardinia stands out as a unique region on the global map in terms of Wilson disease prevalence. In this area, a distinctive founder mutation (441/-427del) is remarkably common, accounting for an impressive 67% of cases. This specific mutation is prevalent to such an extent that all other mutations associated with Wilson disease in the region are relatively rare, each occurring at frequencies below 10%. Consequently, Sardinia has earned recognition as one of the few places worldwide with an exceptionally high incidence of this genetic disorder, highlighting the significance of this specific mutation in the local population.

3) Pathophysiology

The clinical manifestations of the disease can take on various forms, exhibiting a pleomorphic nature [7,8]. Interestingly, despite extensive research, establishing a clear and direct correlation between specific mutations and predominant clinical presentations has proven to be elusive. In other words, while certain genetic mutations are associated with Wilson's disease, the precise way these mutations manifest in individual patients can be highly diverse and challenging to predict. This complexity underscores the need for personalized and comprehensive approaches to diagnosis and management in individuals with Wilson disease and there are significant geographic differences even though the disease's clinical forms tend to cluster [9] Therefore, WD may have a predominance in the hepatic, neurological, or mental systems, and illness symptoms can range from being asymptomatic to having fulminant hepatic failure, which can be fatal [10–14] More than 5% of WD patients in Costa Rica manifest with fulminant Wilson disease (FW), which is characterized by a liver-predominant condition Wilson disease can manifest in various forms of liver involvement, each with its own set of characteristics[4].These liver-related presentations include cirrhosis, acute hepatitis, acute-on-chronic liver failure, and a silent form of the illness characterized by elevated levels of transaminases without overt symptoms. This diversity in liver-related symptoms highlights the complexity of Wilson's disease and underscores the importance of tailored diagnostic and treatment strategies to address the specific manifestations that an individual may experience. When copper is released into the bloodstream, it can lead to a type of hemolytic anemia known as Coombs-negative hemolytic anemia. This condition is characterized by intermittent episodes of mild hemolysis, where red blood cells are prematurely destroyed, and jaundice, which is the yellowing of the skin and eyes due to elevated bilirubin levels in the blood.

Neurological manifestations associated with this condition can be classified into distinct categories, each presenting unique clinical characteristics.

3.1. Akinetic-Rigid Syndrome: This category resembles Parkinson's disease, with individuals experiencing symptoms such as muscle stiffness, reduced movement (akinetic), and a tremor at rest. These features can significantly impact motor function and mobility.

3.2. Pseudosclerosis (Tremor-Ataxia Dominated): In this presentation, the primary symptoms revolve around a combination of tremors and ataxia. Tremors involve involuntary shaking movements, while ataxia refers to difficulties with coordination and balance. This combination can lead to challenges in performing fine motor tasks and maintaining stable posture.

3.3. Dystonic Syndrome: Dystonia is characterized by sustained or repetitive muscle contractions, leading to abnormal postures or movements. In the context of this condition, dystonic syndrome often results in severe muscle contractures, which can limit mobility and cause discomfort or pain [15,16] .These categorizations help healthcare professionals understand and diagnose the diverse range of neurological manifestations associated with this condition. Tailored treatment and management

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approaches are typically developed based on the specific neurological profile and needs of the affected individual.
3.5. Neurological manifestations can be classified into three distinct categories
3.5.1. Akinetic-Rigid Syndrome Resembling Parkinson's Disease: This category is characterized by symptoms resembling those seen in Parkinson's disease.
3.5.2. pseudosclerosis with Tremor and Ataxia Dominance: Pseudosclerosis manifests primarily with symptoms of tremors and ataxia [17,18]
3.5.3. Dystonic Syndrome Leading to Severe Contractures: Dystonic syndrome is characterized by sustained muscle contractions that result in abnormal postures or twisting movements Neuropsychiatric symptoms and signs, such as a decline in scholastic performance, impaired hand-eye coordination, and noticeable behavioral changes, can serve as early warning signs that a more pronounced neurological presentation may be on the horizon [19] These indicators suggest that there may be underlying neurological factors at play, which, if left unaddressed, could manifest in more overt neurological symptoms and challenges. It underscores the importance of recognizing and addressing these initial signs to potentially intervene and provide appropriate care before more significant neurological issues emerge. Additional observations encompass drooling, spasticity (muscle stiffness and tightness), chorea (involuntary, jerky movements), athetosis (slow, writhing movements), myoclonus (brief, sudden muscle twitches), micrographia (small and cramped handwriting), dyslalia (speech difficulties), hypomimia (reduced facial expressiveness), and dysarthria (difficulty in articulating speech). These diverse findings highlight the wide spectrum of potential neurological symptoms and manifestations that can occur in individuals with neurological conditions, underlining the complexity and variability of these disorders. In the initial condition, copper deposition is evident in Descemet's membrane, while in the latter condition, the anterior and posterior capsules of the lens display this deposition. Notably, in both cases, the copper accumulation spares the epithelial and cortical cells. These distinctive copper depositions serve as significant diagnostic markers for the respective conditions, highlighting the specific sites within the eye where this material tends to accumulate Ocular manifestations encompass the presence of the Kayser-Fleischer ring, as well as the development of sunflower cataracts within the lens Sunflower cataracts are less frequently seen in WD, despite Kayser-Fleischer rings being highly common, particularly in individuals with neurological aspects of the illness. Simmerling and off initially identified sunflower cataracts in WD patients with Kayser-Fleischer rings in 1922. They observed a striking similarity between these abnormalities and those caused by the presence of a foreign object containing copper that had become lodged in the eye. With ongoing therapy, pair symptoms could go better. By employing advanced techniques such as corneal confocal microscopy and spectral domain optical coherence tomography, researchers have been able to detect and document instances of small fiber peripheral neuropathy impacting the corneal nerve network and neuronal degeneration affecting the retina. These innovative methods have provided valuable insights into the extent and nature of these neurological conditions, shedding light on their effects on both the cornea and the retina. Up to one-third of patients may exhibit psychiatric abnormalities before hepatic or neurological symptoms. These include personality changes or decreased academic performance, sexual exhibitionism, impulsivity, mood swings, unacceptable conduct sadness, over-sensitive, and mental illness. In a small number of cases, psychiatric abnormalities have also resulted in suicide [20,21]

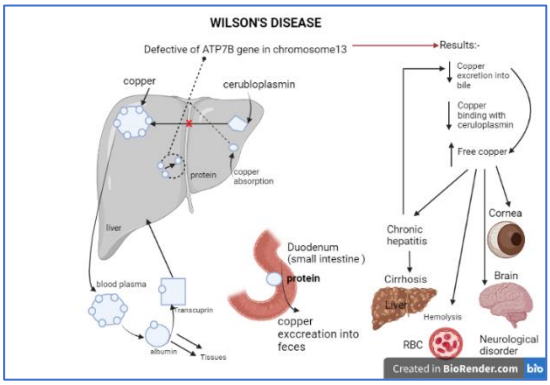

Fig. 3. Kayser-flesher ring

4. Diagnosis

The essential diagnostic components comprise:
(1) Serum ceruloplasmin, usually reduced to approximately 50% below the lower limit of normal, can sometimes be elevated. This elevation can result in a misleading negative outcome in cases of inflammation, as ceruloplasmin acts as an acute phase reactant during such states
(2) The 24-hour urinary copper excretion, typically

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exceeding 100 mcg/24 h in adults and surpassing 40 mcg/24 h in children.
(3) Serum-free copper levels typically exceeding 200 mcg/L.
(4) Hepatic copper levels, typically exceeding 250 mcg/g of dry weight.
(5) The identification of Kayser-Fleischer rings during slit-lamp examination is a significant diagnostic indicator. Nevertheless, it's important to note that these rings might not be present in up to 50% of individuals with hepatic Wilson's disease, often absent in most asymptomatic siblings, and occasionally found in other liver conditions like primary biliary cirrhosis [22].
Another simple diagnostic method involves assessing the relative exchangeable copper levels, which can be determined by examining the ratio of serum exchangeable copper to total serum copper. A ratio exceeding 18.5% indicates a potential issue (CuEXC/CuT). The serum copper/ceruloplasmin ratio (g/Dl) is still the easiest test, though; if it is larger than 2, it indicates the presence of WD, and if it is less than 1, it indicates a good person. While the 24-hour urine test is frequently employed, it may not be convenient and could pose challenges for patients when it comes to collecting the samples. Our group has proposed a six-hour copper, urine test following a D-penicillamine challenge that offers quick diagnosis and high Precision is achieved with a cut-off level set at 118 mcg Cu/6.hr observation for Wilson disease [23].Family screening is recommended since early detection is essential to begin treatment, ideally while the illness is still asymptomatic and before liver decompensation or significant neurological irreparable damage has taken place. The best course of action in this situation end copper studies on the catalog case's immediate family members and close relatives.

5. Current Drug Management:

It is recommended to start treatment as soon as a diagnosis is made in asymptomatic people as soon as a diagnosis is made in symptomatic subjects. When therapy is started on time it is possible to prevent degeneration and maintain a life expectancy similar to that of individuals who are in good health. Therefore, the goals of treatment are to delay the onset of indication in pre-symptomatic people, to delay medical degeneration in sick cases in situations of acute-on-chronic hepatitis, and to avoid death Since WD treatment is lifetime, treatment concepts for it include the formation of a specific diagnosis, monitoring compliance, timely diagnosis of problems, Comprehensive management involves a holistic approach, which includes timely assessment of neuropsychiatric conditions and when needed, the implementation of physiotherapy [24,25]. With the end objective of normalizing free plasmatic copper, therapy is focused on the elimination of excess cup rum with chelator like Cuprimine trientine [22]or tetra thiomolybdate [26] or by limiting intestinal absorption of copper with zinc salts. Since WD is an uncommon ailment, the drug used to heal it falls under the category of a rare disease drug [27] as such, they were not subjected to the same rigorous testing and development procedures as most medications for which data regarding their pharmacokinetics and pharmacodynamics were accessible before they authorized therapeutic use and commercial promotion.

5.1 D-penicillamine

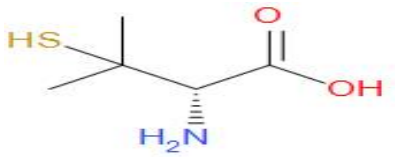

Fig. 4. Structure of D-penicillamine

D-penicillamine, initially used orally to treat WD in 1956, Chelates don't only bind to copper; they can also interact with various other metals. In reality, the first racemate combination that was readily accessible necessitated concurrent administration of pyridoxal to prevent a deficiency of nutrients, even though pyridoxine enrichment is still advised. This medication encourages copper excretion in the urine, but it also stimulates the production of the intracellular chelator metallothionein, which encourages less absorption through fecal elimination D-penicillamine was first used to treat rheumatoid arthritis because it has some immunosuppressive qualities.[28]. Additionally, when this agent messes with how collagen links together, it can cause some problems like slow or not-so-great healing of wounds. However, it can also do some good stuff like slowing down or making better a liver condition called hepatic fibrosis Even though we need more extensive studies and longer observations to be completely sure,

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the final result didn't show any difference. In a closer look at tissues, it seemed that the progression of fibrosis was about the same in patients who were given zinc and those who got D-penicillamine as treatment [29]. Even though some people might experience a temporary worsening of their neurological symptoms between (10% to 50% of patients), this treatment is popular because it's affordable and generally works well. However, there isn't enough solid evidence to prove that it's better than using zinc therapy [30]. You might notice improvements in issues like ascites (abdominal fluid buildup), jaundice (yellowing of the skin and eyes), and how well your liver makes important substances as soon as 2 to 6 months after beginning treatment. If you're dealing with noticeable symptoms, it's usually recommended to begin with a daily dose of 250-500 mg. After that, you can increase your dose by 250 mg every 4-7 days, but don't go beyond a maximum of 1-1.5 grams per day, and it's usually taken in two to four smaller doses throughout the day. A maintenance dose is lower: 750-1000 mg/d administered in two daily doses. In the pediatric population, the recommended dose is 20 mg/kg per day rounded off to the nearest 250 mg and distributed in two or three doses daily, reducing by 25%-30% in maintenance therapy. Since D-penicillamine's absorption is inhibited by food, this medication should be taken either one hour before or two hours after eating. Unfortunately, side effects are rather prevalent with Cuprimine usage and necessitate stopping in 20%–30% of individuals [31,32]. Massive and abrupt increases in free copper following treatment with Cuprimine and other powerful can cause neurological damage, which is often permanent. [33]. Neurological deterioration has been associated with free copper spikes caused by chelators like D-penicillamine The mobilization of significant quantities of free copper, together with a rise in malondialdehydes and a decrease in glutathione, is the mechanism causing neurological deterioration· Additionally, between 2 and 3 months before the planned operation, Cuprimine must be stopped due to its effects on collagen synthesis therefore on tissue repair [34].

5.2Trientine

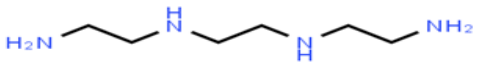

Fig. 5 Structure of Trientine

Syprine, a sequestering agent of various metals like iron, zinc, and copper was created and launched in 1969 as a substitute for a patient client who could not take Cuprimine and promotes the excretion of cuprine through the urine [35]. This substance has good data, making it possible to use it as an initial therapy or an alternative to other pharmacological agents, even in cases of decompensated hepatic vein disease. However, its high cost may make it difficult to use as a first medication, and the clinical information that is currently accessible is imperfect to abandoned studies. Even though it has been noted that neurological symptoms might get worse, this phenomenon seems to happen less frequently than with D-penicillamine. However, there have been reports of neurotoxicity, and clinical research discovered that trientine caused an early neurological decline in about 26% of treated individuals [36]. The administration of two or more drugs with iron should be interrupted, since the resulting complex may promote perniciousness. Cuprine's absence to prompt by Syprine through overutilization can result in Amendable side refractory anemia due to cuprine deficiency and iron overload in the livers of patients with WD, similar to that recognized for Cuprimine [37]

5.3 Zinc

Wilson's Disease (WD) was the first illness for which zinc was used as a treatment in the early 1960s. At first, zinc chloride salt was used for delivering it, but consequently, the zinc sulfate salt [38] was also used for this purpose. But it wasn't until 1978 that it received recognition from the government as a form of treatment. Although zinc acetate is frequently gentler on the stomach, there is little to no difference in the efficacy of the various zinc salts. It differs from the therapies outlined before in that it operates uniquely. It functions by promoting enterocyte metallothionein, a natural

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metal-binding agent within the intestines. This encourages the capture of copper within enterocytes and its subsequent elimination through feces during the regular shedding of intestinal cells. Additionally, zinc might have a beneficial impact by stimulating intra-hepatic metallothionein, potentially providing additional protection for the liver Another potential mechanism of action for zinc involves its capacity to reduce lipid peroxidation and increase the availability of glutathione within liver cells. This, in turn, can help reduce damage caused by oxidative stress. While zinc therapy was initially preferred mainly for maintenance or in asymptomatic individuals, it has proven its effectiveness in gradually achieving a negative copper balance. Consequently, it is now increasingly and effectively used as a first-line treatment option. Originally, zinc therapy was primarily used as a maintenance treatment or for individuals who showed no symptoms of the condition. The recommended amount of elemental zinc is 150 mg/d, split into 3 doses. The dosage for the pediatric group is 75 mg/d, split into three doses. Food interferes with absorption, just like it does with the other pharmacological treatments available to treat Wilson Disease, thus this medication must be taken at least an hour before or two hours after meals. The maximum induction of intestinal metalloproteins happens three weeks after the start of zinc, so whenever the therapeutic decision to switch from chelators to zinc is made, it should be noted that the chelator should be continued for this time period, administered at least an hour before or after zinc. Fortunately, there aren't many side effects of zinc, and those that do tend to be mild and not life-threatening. These include sideroblastic anemia, which can indicate both excessive copper removal and copper insufficient supply, digestion, discomfort, which may subside with time, alcohol bias, headaches, increased sweating temporary rises of plasmatic lipase is amylase, and alkaline phosphatase, among others, and it enhances sweating [39].

5.4 Zinc+trientine

Zinc in combination with oral chelating drugs can be used as a complementary treatment with separate but linked mechanisms of action. Trientine/zinc combination therapy should be adopted as the standard for use as the primary care for hepatic failure in patients with Wilson's disease since Efficaciousness is comparable to or to some extent greater than that of penicillamine while having a significantly lower incidence of side effects. Thus, by using this medicine to treat Wilson disease patients, the need for liver transplantation may be significantly reduced, preserving the supply of liver donors and reducing the liver shortage [40].

5.5. Dimercaprol

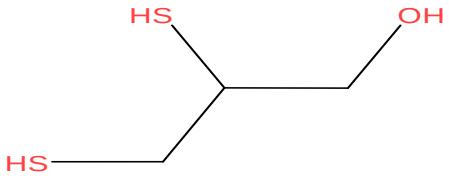

Fig. 6. Structure of Dimercaprol

In 1940, a team led by Sir Rudolph Albert Peters at the University of Oxford in the United Kingdom created dimercaprol (2, 3-dimercapto-1-propanol), also known as British anti-Lewisite (BAL), as an antidote to an arsene chemical weapon called lewisite at the time of World War II.26 'BAL' is an alcohol containing two substituted sulfhydryl groups (dithiol), which along with trivalent arsenic develop a solid five-person ring and reduce its toxicity. BAL was chosen over other dithiols because it was efficient and safe to be applied to human skin and was administered as a series of daily injections, one after the other, for several weeks at a time. These painful subcutaneous injections frequently resulted in abscesses and hematomas at the injection site [41,42]. 50% of patients were found to have negative impacts. The most common symptoms were tachycardia and dependent-on-dose hypertension. Likewise seen were symptoms such as nervousness, agitation, nausea, vomiting, headache, paresthesia, dysesthesias, chest tightness, abdominal discomfort, flushing, and perspiration. Thirty percent of youngsters experienced fever brought on by drugs. Patients with peanut allergy should not use BAL since it is reconstituted in peanut oil. In addition to these problems, the main drawback of using BAL was the development of tachyphylaxis, which was accompanied by dwindling therapeutic advantages and the recurrence of symptoms. That BAL courses are repeated is one reason. Dimercaprol was administered as a series of daily injections, one after the other, for several weeks at a time. These intramuscular injections that sting frequently resulted in abscesses and hematomas at the injection site. 50% of patients were found to have negative impacts. The most common symptoms were

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5.6. Trientine dihydrochloride

The two salts of trientine are trientine dihydrochloride and trientine tetrahydrochloride. Trientine dihydrochloride must be stored between 2 and 8 degrees Celsius since it is unstable at room temperature. It was proclaimed in the UK in 1985 for the treatment of Wilson disease by the Medicines Health and Regulatory Agency (MHRA) and other European nations including France, Germany, and Spain. Due to d penicillamine intolerance by some people, it was utilized as an alternate treatment and administered in hospital pharmacies. The trientine tetrahydrochloride, which may be held at ambient temperature, is the salt that is among them that is the most stable. From the middle of the 1970s until 2009, it was offered as a hospital preparation in France, supplied by AGEPS (Agence Générale des Equipment) [43].

5.7. Tetrathiomolybdate

A crucial micronutrient that exists in food is molybdenum. In the veterinary medical literature, there have long been contributions of sheep getting "heart disease," also known as copper deficiency syndrome, when they graze on grasslands in Australia that are molybdenum- and sulfur-contaminated. Whenever it was established that Wilson's Disease (WD) was caused by copper toxicosis in the 1940s, several studies began suggesting the use of molybdates as a possible therapy for the medical condition. Molybdenum, however, failed to improve patients clinically or biochemically in early research. While the ovine abomasum (fourth stomach) may convert molybdate into tetrathiomolybdate (TTM), it's conceivable that the human gastric mucosa cannot. Likewise, molybdate lacks TTM's anti-copper qualities. Inorganic biochemist Stuart Laurie of the University of Leicester and others examined the use of ammonium TTM, a reduced version of molybdate, as a potential remedy for Wilson's disease (WD) in the 1980s. To explore potential adverse effects, after personally taking the medication for a week without experiencing any side effects, Walshe recommended it to others. By forming complexes with copper and proteins in the gastrointestinal lumen, ammonium TTM (often referred to as tetrathiomolybdate or TTM) administered orally nearly entirely prevents dietary copper absorption, according to radiocopper studies. These complexes are excreted in the feces because the intestinal cells are unable to absorb them. When it comes to inhibiting dietary copper absorption, TTM is more effective than zinc because, unlike zinc, its impact is instantaneous. Both parenteral and oral TTM chelates tissue copper by generating inert complexes with copper and proteins in addition to blocking copper absorption may lessen angiogenesis, fibrosis, and inflammation by suppressing several copper-dependent cytokines, according to oncology research [44,45].

6. Alternative Treatments:

6.1. Ammonium tetrathiomolybdate

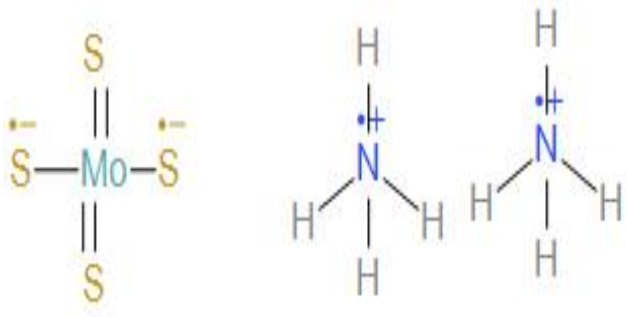

Fig. 7. Structure of ammonium tetrathiomolybdate

Tetrathiomolybdate is a novel copper (Cu)-chelating drug recognized for its antiangiogenic features. Tetrathiomolybdate was developed as a result of the knowledge acquired when dealing with copper toxicity in animals. This mechanism helps to increase copper excretion through urine and feces by chelating copper and promoting the activity of intestinal metalloproteins. Due to its method of action that entails binding to copper while encouraging intestinal metalloproteins, copper disappears from our bodies with greater frequency through the urine and feces. Although it has not yet been

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authorized by the American Food and Drug Administration (FDA), tetrathiomolybdate has been utilized to treat Wilson's disease (WD) in Europe since 2008. Despite the absence of medical proof, it seems that this medicine is effective as well as secure, in particular for those suffering from severe neurological symptoms. The effects of trientine and tetrathiomolybdate treatment on people with neurological Wilson's disease (WD) have been studied in a randomized, double-blind research. Neurological impairment was seen in 6 out of 23 individuals receiving trientine therapy, contrasted to only 1 out of 25 patients using tetrathiomolybdate [46].

7. Treatment In Special Condition

7.1. Fulminant Hepatic Failure

The initial and paramount step in the management of acute liver failure is the rapid recognition and confirmation of the diagnosis [47]. This is particularly crucial in such situations, and there should be a heightened suspicion for this condition when encountering fulminant hepatitis, often occurring suddenly without prior symptoms, Elevated transaminase levels (AST/ALT > 2.2), along with elevated alkaline phosphatase and total bilirubin (total bilirubin/> 4), and an increase in serum total c, are indicative factors to consider. Considering that fulminant Wilson's disease (WD) has been observed more frequently in this specific subgroup of patients, the likelihood of a WD diagnosis becomes even higher when this presentation occurs in young girls aged 11 to 25 and coincides with the onset of puberty. Copper levels in the blood can be significantly reduced through implementing strategies such as fast plasma exchange using an assortment of techniques like plasmapheresis, hemofiltration, antigen dialysis, or transfusion for exchange, these approaches can act as stopgap treatments for patients awaiting liver transplants as well as protecting the kidneys from copper-induced tubular damage. They could potentially be used as a replacement for liver transplantation in instances where it is not feasible. Even though there have been reports of modest improvement, and even though treatment success without transplantation has been verified, the need for liver transplantation is still an essential consideration in many patients. The use of the molecular adsorbent recycling system ultrafiltration device, which combines ion exchange with albumin dialysis, holds the potential to remove copper and achieve clinical stability in such cases. This approach can act as a bridging therapy before liver transplantation [48,49].

7.2 Pregnancy

There have been instances of acute liver failure occurring when the treatment is discontinued during pregnancy [47,48] Therefore, it is imperative to maintain treatment throughout the entire duration of pregnancy to mitigate this risk. Pregnant individuals with Wilson's disease (WD) have been successfully treated using penicillamine, trientine, and zinc salts, yielding positive outcomes for both the mother and the developing fetus. Although it is not definitively established whether trientine can cause birth defects in humans, there is evidence suggesting its potential to do so in animals. [49,50] Additionally, there have been reports of teratogenic effects associated with D-penicillamine in both animal studies and human cases.[51] Identifying a higher risk of birth abnormalities in the Wilson's Disease (WD) patient population is challenging, even though there have been reports of such abnormalities occurring after WD therapy [52,53]. This difficulty arises primarily because the disease itself is rare, making it challenging to draw definitive conclusions regarding the relationship between WD therapy and birth defects. There is little doubt that any prospective harm to the fetus is compensated for to the potential risk of decompensation when therapy is stopped. Therefore, with the right maternal protection, zinc is the greatest remedy for conditions during pregnancy and breastfeeding .[54,55]

8. Conclusion

Wilson's disease is a rare genetic disorder that affects the body's ability to metabolize copper, leading to a dangerous buildup of copper in various organs, primarily the liver and brain. This condition is caused by a mutation in the ATP7B gene, which is responsible for regulating copper levels in the body. The excess copper can lead to a range of symptoms and complications, including liver problems, neurological issues, and psychiatric disturbances. Common symptoms may include fatigue, jaundice, abdominal pain, tremors, and personality changes. Diagnosis typically involves blood tests, liver biopsies, and genetic testing to confirm the presence of the ATP7B gene mutation. Once diagnosed, treatment often involves medications to reduce copper levels and, in severe cases, liver transplantation. Early detection and treatment are essential in managing

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Wilson's disease effectively, as it can be life-threatening if left untreated. Therefore, regular medical monitoring is crucial for individuals with this condition to prevent further complications and maintain a good quality of life. Zinc D-penicillamine, trientine, dimercaprol, trientine dihydrochloride use in Wilson's disease.

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