CLDF
Chronic Liver Disease Foundation

Clinicians and Patients Confront Practical Issues in Wilson Disease

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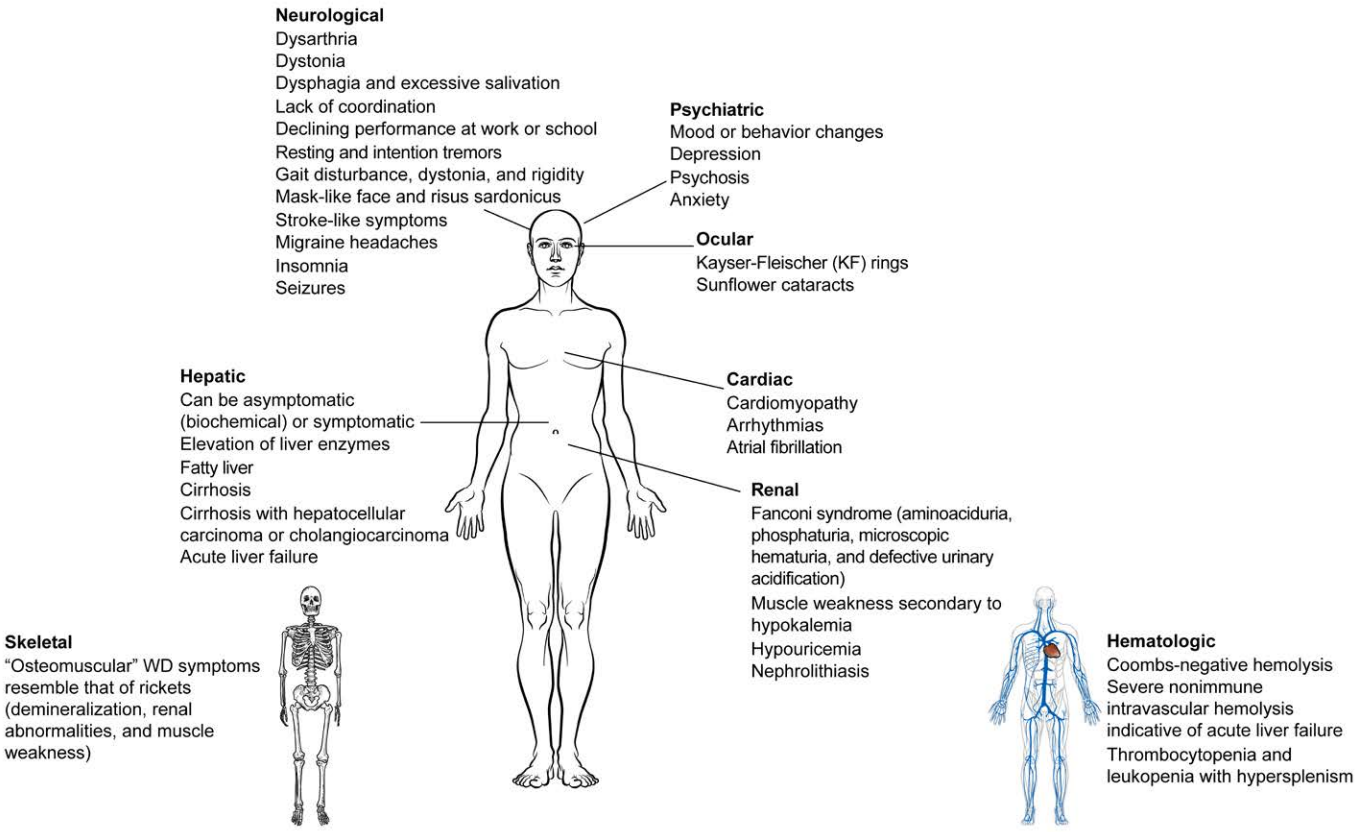
Introduction

Wilson disease (WD), first identified in 1911,[1] is a genetic disease of copper metabolism caused by mutations in the ATP7B gene.[2] WD is considered a rare disorder that can affect males and females in equal numbers and all races, ages, and ethnic groups. Since the major route of copper excretion (95%) is through the liver, excess copper first accumulates there and over time leads to progressive liver damage (fibrosis and subsequently cirrhosis). Copper accumulation eventually spills into the blood and impacts numerous organ systems, especially the liver and central nervous system, including the eyes (Figure 1). Although only about 2,000 to 3,000 cases have been diagnosed in the United States, other affected individuals may be misdiagnosed with different liver, neurological, or psychiatric disorders.[2] WD affects nearly 1 in every 30,000 people worldwide[3] and, with the US population at about 340 million, this indicates that approximately 10,000 patients in the United States have WD.

Figure 1. Several Organ Systems Impacted by Wilson Disease[4]



This disease is progressive and, if left unidentified and untreated, may cause chronic liver disease leading to cirrhosis, neuropsychiatric dysfunction, and death. Due to the rarity of WD, multisystemic involvement and clinical heterogeneity, it is difficult for a single practitioner to develop sufficient expertise to diagnose and treat WD through clinical experience alone.[5] WD is often difficult to detect as its signs and symptoms are frequently mistaken for other conditions or diseases.[6] Early diagnosis of WD is crucial to ensure that adequate treatment can be started, which can lead to a full and normal life. Although most patients respond to early institution of appropriate therapy,[7] in some patients, WD is associated with considerable disability, the need for liver transplantation, and death.[1, 8] This indicates that there are unmet needs associated with this disease.

"With over 100 years of having this disease identified and 4 available treatments, patients should not be slipping through the cracks"

Rhonda Rowland, Patient with WD, Patient Advocate and President of the Wilson Disease Association.

Goals of the Whitepaper and Author Perspectives

In 2022, the American Association for the Study of Liver Diseases (AASLD) set forth practice guidance on the diagnosis and treatment of WD, which replaced the previous 2008 guidelines.[9, 10] In 2023, the Chronic Liver Disease Foundation (CLDF) published a summary of the updated AASLD Practice Guidance,[4] in which the authors reviewed and commented on the latest recommendations and provided evidence-based and practical tools for clinicians who manage WD. This whitepaper seeks to further build upon the success of these publications and is geared toward the practical issues facing providers caring for patients with WD, including:

- Strategies to improve the diagnosis of WD
- Establishing safe, effective, and accessible treatment strategies
- Identifying and overcoming adherence and compliance challenges
- Understanding individual patient needs and building rapport

As with the previous two publications, the goal of this whitepaper is to ultimately improve the long-term outcomes for patients with this disease.

As depicted in Figure 1, the presentation of WD is clinically heterogeneous and can involve many organ systems. Therefore, in most instances, the way the disease presents in a patient dictates who ultimately diagnoses WD. For example, a patient with neurological symptoms will be directed to a neurologist, whereas an asymptomatic patient with abnormal liver function tests will be referred to a hepatologist. Furthermore, although the age at WD presentation is considered mainly between 3 and 55 years old, it is actually "both younger and older than generally appreciated."[4] Patients with WD can therefore be diagnosed and managed by clinicians of different specialties and with expertise in patients of various ages. As such, clinicians across multiple disciplines have collaborated to write this whitepaper (See Box 1). In addition, a patient with WD, who is also a patient advocate and the president of the Wilson Disease Association, has provided a patient's perspective on her experience with the disease.

Box 1. About the Authors of and Contributors to this Whitepaper

Regino P. Gonzalez-Peralta, MD, is a specialist in pediatric hepatology who treats WD in children younger than 21 and adults and serves on the WD Association Advisory Committee. Children with undiagnosed WD most often visit his practice with abnormal liver tests and he usually identifies WD after detecting low ceruloplasmin. His adult patients are typically established patients with WD who are seeking a disease expert to provide maintenance care. Dr. Gonzalez-Peralta builds an "incredible rapport" with his patients having cared for them through their journey from young children accompanied by their parents, to teenagers facing adolescent issues compounded by a chronic liver disease diagnosis, to young adults seeking college degrees and ultimately starting their adult lives. In his office, Dr. Gonzalez-Peralta works closely with ***Jordan Perno, BSN, RN***, who, in addition to providing thorough patient care, assists patients in other essential areas, such as WD medication access.

Sammy Saab, MD, is a hepatologist who diagnoses and treats WD in adult patients. In his practice, Dr. Saab works closely with ***Sherona Bau, NP***, an advanced practice provider who specializes in hepatology. Both are independent providers, and their patients with WD have hepatic manifestations on presentation but are otherwise asymptomatic, unless they are at the point of decompensation. In their clinic, Dr. Saab and Ms. Bau diagnose and treat WD in new patients and provide maintenance care for established patients with WD.

Jeff Bronstein, MD, PhD, is a neurologist who sees a mix of patients with WD in terms of symptoms and ages and directs the WD Association Center of Excellence. He also serves on the WD Association Medical Advisory Committee. In his experience, Dr. Bronstein reports that approximately 50% of patients with WD will have neurological and/or psychiatric symptoms on presentation. They may suffer from a long list of neurological symptoms, with the most common being dysarthria (change in voice), dystonia (abnormal contractions of movements), and tremors. Other symptoms can include ataxia, difficultly walking, gait disorders, Parkinsonism, and seizures. Depression, anxiety, and cognitive impairment are also common in patients with WD. Brain MRI results are usually abnormal in patients with WD who have neurological symptoms. Abnormalities of the brain usually involve the basal ganglia.

Rhonda Rowland is a patient with established WD. In 1983, as a senior in college, Ms. Rowland went into liver failure and, because she presented with a low-end-of-normal ceruloplasmin, was initially misdiagnosed with chronic active hepatitis. After her liver biopsy showed high levels of copper, and an ophthalmologist referral led to the detection of Kayser-Fleischer rings, the diagnosis of WD was made. Despite living with WD for more than 40 years, Ms. Rowland has had a successful career at CNN as a medical correspondent and in freelance medical communications and, in recent years, has focused her attention to WD. She has interviewed Dr. John Walshe, discoverer of D-penicillamine, is working on a book about her experiences and in 2020 joined the board of the Wilson Disease Association, where she currently serves as president. Ms. Rowland is well-controlled on WD medication and considers herself one of the "lucky ones", but has observed WD patients receive liver transplants and experience severe liver, neurologic and psychiatric complications and become emotionally impacted as a result of this disease. Ms. Rowland is doing what she can to raise awareness so other WD patients can avoid these types of outcomes.

Strategies to Improve the Diagnosis of WD

If WD is diagnosed and treated early, patients can achieve normal life expectancy.[7] According to the AASLD guidelines, WD should be considered when a patient has one or more of the following on presentation: liver abnormalities of uncertain cause, regardless of age; unexplained liver disease associated with neurological or psychiatric disorder(s); acute liver failure with hemolytic anemia; or recurrent, self-limited, autoimmune hepatitis. A gold-standard test to confirm WD does not exist. Therefore, after a thorough history and physical examination, a combination of the following is recommended: liver biochemistries; complete blood count and international normalized ratio; serum ceruloplasmin; basal 24-hour urinary copper excretion; slit-lamp or optical tomography examination for Kayser-Fleischer rings; a neurological evaluation; and a molecular genetic investigation of ATP7B.[4, 9, 10] In selected cases, a liver biopsy will be performed to confirm the diagnosis of WD.

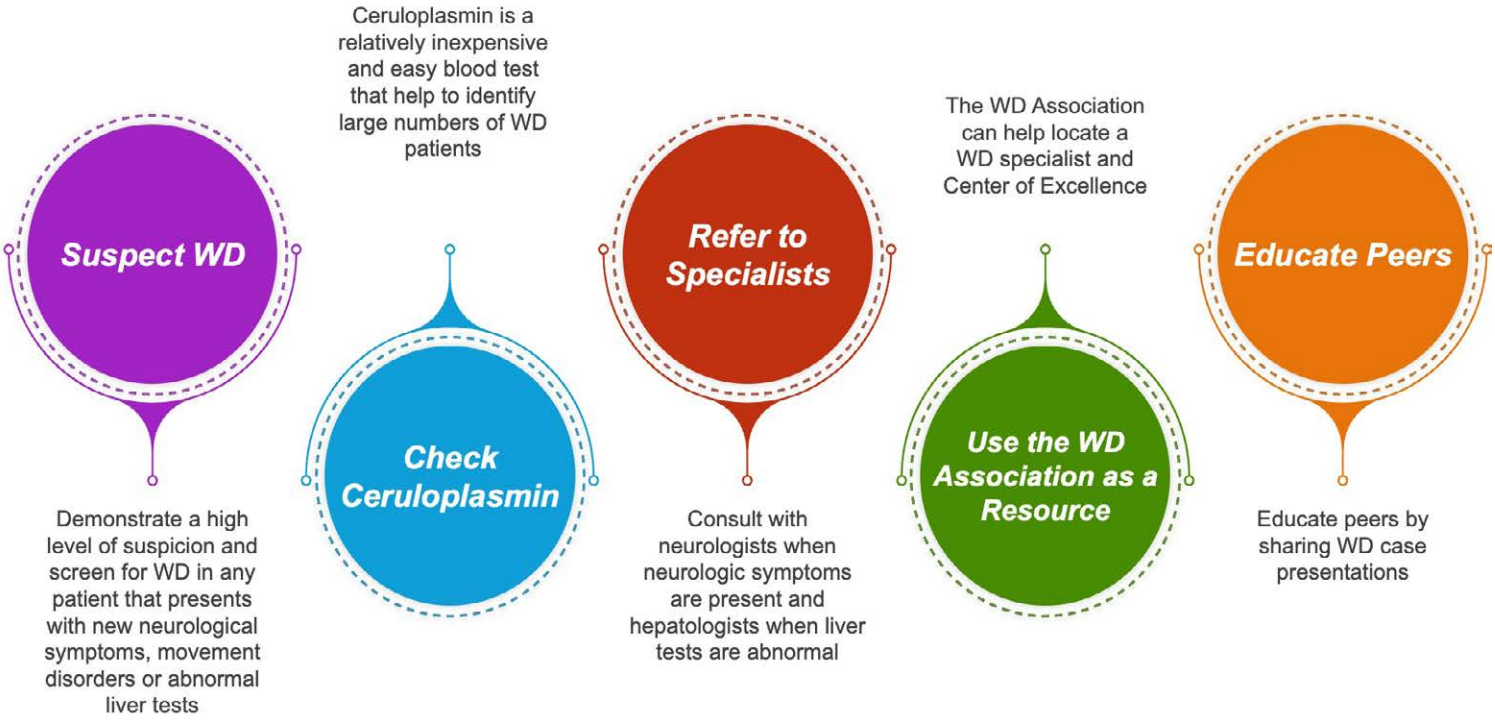
Despite these recommendations, patients with WD may experience inaccurate or late diagnoses.[11, 12] One study noted that 72% (129/179) of patients with WD were misdiagnosed with hepatitis, cirrhosis, splenomegaly, hepatomegaly, encephalitis, encephalopathy, peripheral neuropathy, psychosis, osteoarthrosis, nephrosis and anemia.[12] The authors reinforce that these data are seen in their clinical practice, where WD diagnoses are often missed or "brushed off," and added that they have seen WD misdiagnosed as metabolic dysfunction—associated steatotic liver disease, autoimmune hepatitis, chronic hepatitis, stroke, Parkinson's disease, multiple sclerosis, and even dental disorders due to neurological mouth manifestations. One major problem is a misdiagnosis of depression, particularly in teenagers. These patients are not correctly diagnosed until they eventually experience severe WD symptoms.

Increased awareness of WD is imperative for making an early diagnosis and for treatment. This is, however, a simple concept that is difficult to achieve. Keeping up with medical knowledge is demanding, and rare diseases rarely attract attention. Hepatology guidelines/guidances exist for WD, but there are no WD guidelines for neurologists. Case presentations of WD can make a profound impact on clinicians and, as such, a case study is included here (Box 2). In addition, Figure 2 illustrates some steps for improving WD diagnoses.

Box 2. Wilson Disease Case Study

Mary is an example of a patient with WD whose condition was misdiagnosed. Mary was 18 years old when she moved away from home to begin her college studies. After 2 months, Mary became very depressed and returned home for winter break. Her primary care physician (PCP) attributed the depression to the stress from her current circumstances and prescribed an antidepressant. Although Mary's depression improved, she developed a tremor. Blood tests revealed mild liver enzyme abnormalities. Her PCP attributed these findings to the antidepressant and made no changes. Nine months after her first complaint of depression, Mary started falling and ended up in the emergency room. There, they noted an abnormal brain MRI and detected compromised liver function. Upon admission, common causes of liver disease were ruled out, and Mary received a diagnosis of viral syndrome. She was discharged from the hospital to a rehabilitation facility where a neurologist reviewed the MRI and considered the diagnosis of WD, which was quickly confirmed with blood and urine tests. After 6 months of chelation therapy and rehabilitation, Mary recovered almost completely and was able to return to college.

Figure 2. Methods to Improve the Diagnoses of Wilson Disease



Establishing Safe, Effective, and Accessible Treatment Strategies

All patients with a newly established diagnosis of WD should be initiated on lifelong medical therapy. Pharmacotherapy of WD involves lowering copper load, which is achieved either by blocking intestinal copper absorption with zinc or facilitating urinary excretion of copper with copper chelators trientine or D-penicillamine.[4, 10] Zinc was traditionally reserved for the maintenance treatment of WD, but is now recommended by the AASLD as a first-line therapy for asymptomatic patients,[4, 10] including children identified during family screening. This is because zinc eliminates copper at a much slower rate than chelators, making it more suitable for patients who are not affected by WD symptoms. Zinc, available in prescription and over-the-counter formulations, is more accessible and affordable than chelating agents. However, patients may complain of gastrointestinal adverse effects (nausea, in particular) and should be counseled to take zinc on an empty stomach. Patients who take over-the-counter zinc should be advised that for WD, a daily dose of 150 mg of elemental zinc is required. There are many formulations available, which can cause confusion. For example, the 220 mg formulation of zinc contains only 50 mg of elemental zinc, so patients with WD taking this formulation require 1 tablet, 3 times daily.

Chelation therapy with both d-penicillamine and trientine increases free copper and can cause early worsening of neurological symptoms in a small subset of patients, with the risk of patients deteriorating before they improve.[13] Chelating slowly appears to reduce the risk, but this has not been well tested and therefore not completely established as a mechanism.

Both D-penicillamine and trientine are effective copper chelators but since trientine has fewer systemic side effects and is thought to have a lower risk of neurological worsening, it is considered the chelator of choice by most WD experts. When administering trientine, begin at 20 mg/kg/d (to 2000 mg/kg/d daily maximum) in 2 to 3 divided doses and incrementally increase the dose over 2 to 3 weeks. D-penicillamine should be started at 250 to 500 mg/kg/d and increased by 250 mg increments every 4 to 7 days to about 1,000 to 1,500 mg/d (15-20 mg/kg/d to a maximum of 2,000 mg/d) in 2 to 4 divided doses.[4]

Some patients experience intolerance to D-penicillamine, such as worsening neurological symptoms, skin and kidney manifestations. and bone marrow suppression. Ms. Rowland chronicled that, despite 21 years of successful disease control with D-penicillamine treatment, she discontinued the medication due to skin changes in her neck, which personally affected her given her profession as an on-air medical correspondent. Ms. Rowland switched to zinc gluconate, since D-penicillamine can be linked to dermatological issues[14, 15], and has remained well-controlled for the past 20 years without gastrointestinal adverse effects. Other patients have experienced safe and effective control of their WD on long-term D-penicillamine and should remain on that treatment.

Trientine hydrochloride, the original formulation, must be refrigerated at all times or the drug potency is lost.[16] Patients often point out that this is particularly stressful when navigating through airport security. Dr. Saab shared a story about a patient with WD taking trientine hydrochloride. While traveling to India, the patient had to request ice from the flight attendants to maintain the correct temperature to store his medication. Patients with WD also report that trientine hydrochloride is sometimes not shipped properly and arrives in a pool of melted ice.

A new formulation, trientine tetrahydrochloride, was approved by the Food and Drug Administration in 2022 as a maintenance therapy for adults with stable WD who tolerate D-penicillamine.[4, 17] Trientine tetrahydrochloride offers the advantage of twice daily dosing and refrigeration is not required,[18] allowing patients the convenience of carrying a chronic medication in their purse or pocket rather than a cooler. Although this new formulation has been described as a "game changer" and a specialty product, prescribers of trientine tetrahydrochloride may need to take extra steps in order to access the medication. (For additional details, visit: https://www.cuvrior.com/patient-support/).

If insurance authorization is denied for any WD medication, it is resourceful to have a medical necessity letter template on-hand to facilitate the appeal to the insurance company. Appendix A provides a table with a list of details that should be included in the letter. This table can be printed and used to collect information for each patient appeal.

Identifying and Overcoming Adherence and Compliance Challenges

There is considerable patient variability in regard to WD medication compliance. This is particularly common with asymptomatic patients and teenagers, but can also occur with patients who have experienced decades of disease control with chronic medication compliance. Noncompliance from WD treatment is different from that of other diseases. In conditions like diabetes or depression, a missed dose or two can result in the return of severe symptoms, whereas in WD, lack of compliance does not translate to an immediate symptom recurrence. Progression comes on so slowly that patients are unaware of how sick they are becoming.

Clinical experience has demonstrated that the more convenient the medication regimen, the more likely the patient will be to adhere to it. For example, Ms. Rowland said that in her experience, because zinc typically needs to be taken three times daily either one hour before or two hours after a meal, the mid-day dose is most frequently (and unintentionally) missed. This was especially true when traveling for work or staying at home with her children, where her routine may change each day. Furthermore, patients, especially those who are frequently on the go or working out of the home, are more likely to be compliant with medications that are easiest to transport, such as those stored at room temperature. Appendix B provides a patient checklist to simplify adherence and compliance which can be printed and distributed to patients. As summarized in Appendix B, recommending visual and auditory cues to remind patients to take their medication can also be very helpful. For example, rather than storing medications in the cupboard or medicine cabinet, patients can create visual cues by placing the bottle next to places in the home that are frequently visited during the daily routine (eg, by their toothbrush or next to the stove). Smartphone or watch alarms can serve as useful auditory cues throughout the day.

Basal 24-hour urinary copper excretion is an important aspect in the diagnosis of WD and requires 6-to-12 month, or even more frequent, monitoring while on treatment.[4, 10] Adherence to this laboratory test is a big issue in WD. Collecting a full day of urine is challenging, particularly in younger patients, but this is currently the only method to estimate treatment

response and compliance. Novel assays are being studied to replace the 24-hour collection, but none are commercially available.[17, 19] In the meantime, clinicians can provide clear instructions and helpful tips to make this easier for patients (Appendix B). Urine collection is difficult to store at work, so patients can be advised to choose the easiest day of the week to perform the test; most patients choose Sundays. All urine produced that day needs to be collected. If this is done incorrectly, they will need to repeat the test. Once patients need to repeat the test, they are usually more compliant and mindful of potential errors. WD researchers are pursuing blood-based copper tests, which are currently being studied,[17, 19] to replace this standard yet cumbersome approach.

Understanding Individual Patient Needs and Building Rapport

Adherence and compliance challenges with medications and lab tests can ultimately lead to patients lost to follow-up. Improvement requires heightened clinician awareness, an understanding of patients' individual situations and needs, and effective strategies. This can be hard to navigate in a busy clinical practice: It is comparable to opening Pandora's box, which by definition means this may bring up great troubles and emotions (family problems, divorces, abuse), but also holds hope. This "box" needs to be opened if you want to treat the patient wholistically.

Factors that affect adherence and compliance change as patients transition through life. Patients who receive a WD diagnosis at a very young age tend to have families who are very involved in their care. Parents or caregivers act as the primary advocate and decision-makers; therefore, adherence to the necessary steps in a patient's care is more likely. Furthermore, siblings of patients with WD are typically screened for the disease as well, so caregivers may be experienced in dealing with WD in more than one child. The transition to adolescence can be a tumultuous time for patients, with cognitive and physical changes, peer pressure, and yearning for conventionality. Chronic medication requirements for any disease are particularly difficult in adolescents and college-aged patients. Although some executive functions aren't fully formed until after 22 years of age[20], young patients with WD are faced with adult responsibilities and consequences. Adherence may become a point of contention between the parent/caregiver and the patient. Parents report concerns with the transition to college, since they are not there to help ensure their children with WD continue to comply with treatment. Improvements in adherence are expected as patients transition to adulthood, but this isn't always the case. Young adults may bypass regular physical examinations and laboratory assessments. Also, young adults are sometimes uninsured (as they lose parental coverage into their late 20's) and, as previously discussed, are not immediately feeling the benefits of treatment or the consequences of noncompliance.

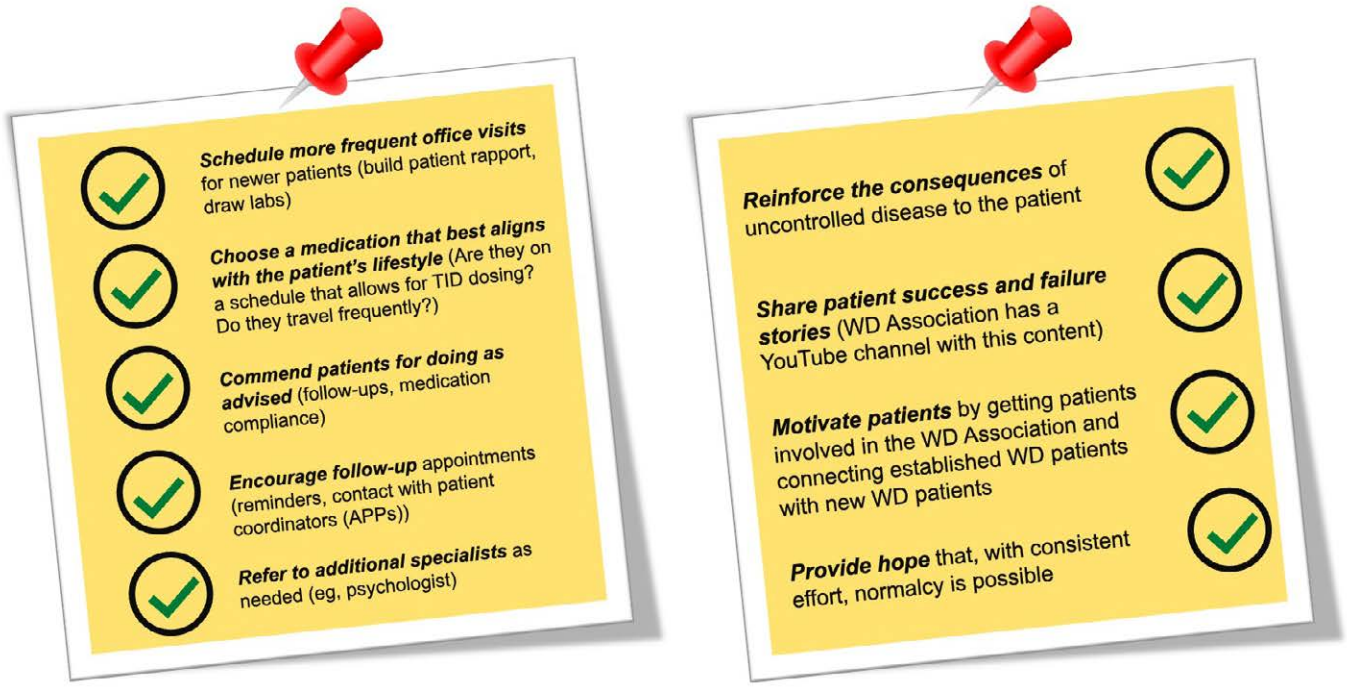
The more rapport the clinician has with the patient, the more successful the results. Some clinicians see patients more frequently to build that relationship. At that time, laboratory samples can be drawn and patients can be shown the physical consequences of treatment noncompliance (eg, elevated liver function tests). Understanding the patient's unique needs can help with rapport. For example, communication with teenagers may be more effective one-on-one, with the caregiver stepping out of the room. Battling with adolescents tends to be unsuccessful, whereas demonstrating empathy for their situation and providing realistic advice is helpful. They can be reminded that their friends don't need to know their diagnosis and medications can be passed off as a "vitamin" or taken privately in the early morning and late at night. In some cases, patients of any age may experience anxiety, depression, and coping issues that accompany this type of diagnosis and a psychiatry referral may be appropriate.

Figure 3 summarizes some of the points mentioned above and provides additional strategies to build patient rapport and promote adherence and compliance. Patient motivation to comply with treatment often comes from connecting with other patients with WD via the WD Association. Some patients are willing to share their stories with fellow patients who have WD. Hearing about how others have coped with WD treatment successes and

failures can also promote compliance. These types of stories and additional resources can be found on the WD Association YouTube channel (https://www.youtube.com/c/wilsondiseaseassociation).

Ms. Rowland said that her early encounters with patients who had severe WD and their families, where the consequences of uncontrolled disease were evident, was a "wakeup call" that made her even more dedicated to keeping her own disease under control. At present, she complies with zinc treatment and her WD is monitored twice a year by a general practitioner and annually by a hepatologist. Imaging studies, including transient elastography, ultrasound, and magnetic resonance imaging, demonstrate no evidence of cirrhosis. Keep in mind that this monitoring is specific for Ms. Rowland and the approach may vary in other patients, depending on how their disease presents (eg, liver vs neuropsychiatric disease), and the stage of the disease. Regardless, providers should commend patients like Ms. Rowland who comply with treatment by recognizing their efforts and successes.

Figure 3. Strategies to Build Patient Rapport and Promote Adherence and Compliance



Conclusions

Prior to Ms. Rowland receiving a diagnosis of WD, she experienced cirrhosis and liver failure. Originally her disease was misdiagnosed as chronic active hepatitis, and she was told that she was very sick and her life expectancy was uncertain. When she received the correct WD diagnosis and was told this disease could be controlled with life-long treatment, the "hope of normalcy" motivated her. "I felt normal and because of that, I felt that I could go on living my life." Early access to diagnosis and treatment from a skilled professional can provide this type of hope to all patients with WD. In the future, more accessible genetic testing, simpler follow-up assessments, and novel, convenient treatments can push us further toward this goal.

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Appendix A: WD Medication Insurance Appeal Letter Details

Background Details	
Date	
Patient name	
Patient date of birth	
Insurance authorization number	
Drug requested, dose, number of tablets, days' supply requested	
Proof-of-Diagnosis	
Age at diagnosis	
Initial presenting symptom(s)	
How the WD diagnosis was established (include at least 3 of the following: low ceruloplasmin, elevated 24-hour urine copper, elevated liver tissue copper, Kayser-Fleischer rings, positive genetic test for ATP7B)	
Patient Clinical Background	
Use and failure of other WD agents, if applicable Treatment failure is indicated by >500 µg/24-hour urine copper, >25 µg/dL of non-ceruloplasmin-bound copper, elevated AST and ALT)[10]	
Patient Clinical Notes and Summary of Laboratory Results	
Relevant clinical notes	
Lab results	
Genetic tests	

Appendix B: A Patient Checklist to Simplify Adherence and Compliance

Visual Medication Reminders

- ☐ I have placed my medication in a place that I frequent throughout the day (next to my toothbrush, near my oven)

Auditory Medication Reminders

- ☐ I have set an alarm on a device that is with me throughout the day (my smartphone, my watch)

24-Hour Urine Collection

- ☐ I have chosen the easiest day of the week for me to perform my test
- ☐ All the urine that I produced that day needs to be collected