

Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment

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Abstract: Wilson's disease (WD) is an inherited metabolic disorder related to disturbances of copper metabolism, and predominantly presents with liver and neuropsychiatric symptoms. In most cases it can be successfully treated with anti-copper agents, and both liver function and neuropsychiatric symptoms typically improve. Treatment guidelines for WD include recommendations for anti-copper treatment as well as for the treatment of liver failure symptoms. Recently, recommendations for treatment of the neurological symptoms of WD have also been proposed. Although most WD patients present with psychiatric symptoms at some stage of the disease, currently there are no guidelines for the treatment of the psychiatric manifestations. Treatment of the psychiatric symptoms of WD is often guided by general psychiatric experience, which typically glosses over the specificity of WD, and can result in severe neurological and/or hepatic complications. Here we review and discuss the possible treatments available for the mood disturbances, psychosis, behavioral and cognitive disorders that can occur in WD, as well as their efficacy.

Keywords: behavioral disturbances, cognitive deficits, mood disturbances, psychiatric symptoms, psychosis, treatment, Wilson's disease

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Introduction

Wilson's disease (WD) is a genetic disorder of copper metabolism that leads to copper accumulation in various organs, primarily the liver and brain.¹ The clinical symptoms are a result of organ dysfunction due to the direct or indirect effects of copper accumulation.^{1,2} WD is typically described as a hepato-neurological disease, leading physicians to focus on signs of liver disease and extrapyramidal symptoms (e.g. tremor and dystonia).^{1,3–5}

WD is known primarily as a liver disorder, as its underlying mechanism includes failure of copper transport in hepatocytes with subsequent impairment of incorporation into the ceruloplasmin and excretion into the bile and blood, and the most frequently presenting symptoms of WD are related to the liver.^{1,6} Up to 60% of patients

present with hepatic symptoms at diagnosis, and up to 100% have at least subclinical laboratory signs of liver damage over the course of the disease. However, copper accumulates in multiple organs over the course of WD, leading to a variety of clinical manifestations, including neurologic (40–50% at diagnosis), psychiatric (10–25% at diagnosis, and up to 100% over the disease course), ophthalmologic (Kayser–Fleischer ring and sunflower cataract) and occasionally endocrinologic, cardiologic and/or osteoskeletal (0–10% of patients at diagnosis symptoms) (Table 1).¹ Psychiatric symptoms occur in almost 100% of WD patients over the course of the disease, and they can present as a variety of disturbances, including affective, psychotic, behavioral, personality, anxiety and cognitive, among others.^{1,7–10} This may necessitate both psychiatric examination and specific treatment.

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Table 1. The most often clinical manifestation of WD and its frequency at disease diagnosis.

WD presentation and its frequency	Symptoms
Hepatic (40–60%)	Asymptomatic elevation of liver enzymes (aminotransferases) Acute hepatitis (jaundice, abdomen pain, etc.) Acute liver failure (coagulopathy, jaundice, encephalopathy) Liver cirrhosis symptoms (compensated or decompensated) (fatigue, spider naevi, portal hypertension, splenomegaly, bleedings)
Neurological (40–50%)	Involuntary movements (tremor, dystonia, ataxia, ballism, chorea, parkinsonian syndrome) Speech disturbances: dysarthria (extrapyramidal, dystonic, cerebellar, mixed, unclassified) Dysphagia Autonomic dysfunction (salivation, electrocardiographic abnormalities, orthostatic hypotension, etc.) Gait and balance disturbances
Psychiatric (10–25%)	Personality disorders (abnormal, antisocial behavior, irritability, disinhibition, etc.) Mood disorders (bipolar disorders, depression, suicidal attempts) Psychosis and other psychiatric alterations (rarely: psychosis, anorexia, sleep disturbances, etc.) Cognitive impairment
Ophthalmologic (K-F ring: 90–100% in neurologic patients, 40–50% in hepatic and 20–30% in presymptomatic); SC (1,2–25%)	Kayser–Fleischer ring (K-F ring); sunflower cataract (SC)
Other (lack of systematic multicenter data, mostly case reports, series reports, or single-center studies)	Renal (tubular dysfunction, nephrolithiasis and nephrocalcinosis, aminocyturia, hypercalciuria, hyperphosphaturia) Bone (osteoporosis, chondrocalcinosis, osteoarthritis, joints pain) Heart (cardiac arrhythmia, cardiomyopathy, myopathy) Skin (hyperpigmentation of lower legs, azure lunulae ('sky-blue moon') of the nails, anteroderma, xerosis, acanthosis nigricans, subcutaneous lipomas, dermatomyositis) Hematopoietic system (thrombocytopenia, hemolytic anemia, leukopenia) Gynecological abnormalities (menstrual irregularity, delayed puberty, gynecomastia) Endocrinological abnormalities (glucose intolerance, parathyroid insufficiency, disorders of growth)

According to international guidelines, WD can be successfully treated with anti-copper agents (chelators or zinc salts).^{1,11} However, some WD patients require treatment with additional drugs that target the problems that can arise over the course of WD, such as symptoms of liver failure (portal hypertension, coagulopathy, pancytopenia), skin changes, neurological symptoms including dysphagia,

tremor, dystonia and sialorrhea, and psychiatric symptoms.^{1,12–14} While treatment of the hepatic and neurological symptoms of WD has been established and there are published international recommendations for the general management of WD, liver failure, and transplantation, there are currently no recommendations for the management of psychiatric symptoms associated with WD.^{14,15}

In the central nervous system, WD predominantly affects the basal ganglia (BG),¹⁶ suggesting that the neuropsychiatric symptoms could be similar to those occurring in other neurodegenerative disorders that involve the BG (e.g. Parkinson's disease, Huntington disease [HD]) and for which there are recommendations for psychiatric treatment.^{17–23} There could also be a common mechanism for some of the behavioral changes, mood disturbances, and anxiety syndromes seen in patients with BG disorders,^{16,24–26} and the involvement of the same neurotransmitter systems (e.g. dopaminergic, noradrenergic, serotonergic) in different disorders could lead to similar recommendations for pharmacological treatment.^{15,27} However, liver involvement should be taken into account in WD, necessitating special safety measures for drugs that are metabolized in the liver. Recent data also suggest that some established psychiatric treatments might be less effective for diseases of the BG.

As is the case with many rare diseases, there is a clear need to establish complex recommendations for the multidisciplinary treatment of WD that also include psychiatric management. As in all chronic somatic illnesses, the presence of psychiatric comorbidity negatively affects outcome, treatment compliance and quality of life. Here, we aim to review and discuss the management of the psychiatric manifestations in WD patients, based on the available medical literature.

Psychiatric symptoms of WD

The most comprehensive review of the psychiatric aspects of WD was published 3 years ago.¹² Ninety articles from the period 1946–2012 were included, and of these 57 were case reports, 12 were cohort studies, 3 were case–control studies and 4 were case series. The authors concluded that psychiatric symptoms can occur before, concurrent with or after the diagnosis and treatment of WD. In their review, 20% of patients had seen a psychiatrist prior to their WD diagnosis, and 30–40% had psychiatric manifestations at the time of diagnosis.

Epidemiological data suggest that up to 30% of WD patients initially manifest with psychiatric symptoms.¹ The first psychiatric manifestation of WD could occur in childhood and appear as a decline in school performance, inappropriate behavior or impulsiveness.^{1,12} Clinical symptoms are often nonspecific, causing difficulties in

diagnosis, including misdiagnoses (isolated obsessive-compulsive disorder or anorexia nervosa, for example).^{28,29} It is common to observe classic psychiatric syndromes in later early adulthood, including behavioral and personality changes,³⁰ anxiety, depression,³¹ manic and hypomanic syndrome,^{10,32–34} cognitive deficits,^{35–39} sleep problems (dyssomnias)^{30,40} and sexual dysfunctions including excessive sexual drive.⁴¹ Some patients also have substance abuse problems,^{42,43} and the presence of a harmful use or dependence syndrome could further complicate the clinical presentation and lead to a delay in the diagnosis of WD.^{1,9}

Most patients develop at least one of the above psychiatric symptoms over the course of the disease; however, the specifics are variable between authors.^{9,44–46} In 1912, S.A. Kinnier Wilson described so-called 'mental' symptoms in 66% (8/12) of WD patients.³ Later studies performed by other groups documented that, apart from liver and neurologic symptoms, psychiatric symptoms are the primary clinical presentation in WD.¹ Svetel and colleagues⁴⁶ found psychiatric symptoms in 72% of WD patients, Akil and Brewer⁹ in 65%, Kumar and colleagues⁴⁴ in 60%, Dennig and Berrios⁸ in 51% and Portala and colleagues³⁰ in 46% of patients. Scheinberg and Sterlieb⁴⁷ stated that every symptomatic WD patient suffers from some kind of psychopathology.

Since the etiology of the psychiatric disturbances occurring in patients with WD can be classified as secondary to the somatic and brain pathology of the disease, it fulfills the criteria of ICD-10 F06, 'mental disorders due to brain damage and dysfunction and to physical disease' (e.g. psychotic, mood disorders) or F07, 'personality and behavioral disorder due to brain disease, damage and dysfunction'.^{48,49} The BG are a structure capable of generating diverse psychiatric syndromes under dysfunctional conditions.^{16,25}

On the other hand, a comorbidity of psychiatric illness (such as major depressive disorder or bipolar disorder) and WD could also be considered, particularly in cases of an established family history of a given psychiatric illness. In such cases, the patient should be coded by both WD and the psychiatric illness. Unfortunately, practically speaking we do not have data elucidating the difference between psychiatric manifestations in the prodromal phase, after initiation of de-coppering treatment, and in successfully treated or chronic

WD patients. Some clinical observations suggest that acute psychiatric symptoms can manifest following initiation of anti-copper agents or in the first few months of treatment, paradoxically even as the neurological status of the patient is improving.^{9,50}

In the end, the treatment of psychiatric disturbances either secondary to or comorbid with WD is generally similar, including basic WD treatment and treatment of the symptoms of psychiatric disturbances, taking into account the limitations of pharmacotherapy due to the liver impairment associated with WD.

Mood disturbances in WD and their treatment

Mood disturbances are the most common psychiatric manifestation in WD. Between 20% and 60% of WD patients develop depression over the course of the disease, with a high rate of suicide attempts, ranging between 4% and 16% of WD patients.^{7,10,12,46,51} The high frequency of depressive syndromes found in WD could be facilitated by the reaction of the patient to the chronic disease state, as well as to physical incapacity related to neurological deficits. Mechanistically, serotonergic deficits in WD can be visualized as a decreased density of presynaptic serotonin transporters in the BG, thalamus and hypothalamus by single-photon emission computed tomography (SPECT).^{1,12}

All available antidepressant drugs, including tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin antagonist and reuptake inhibitors (SARIs), as well as electroconvulsive therapy (ECT) have been successfully used in the treatment of depressive syndromes in WD.^{12,14,15,52–54} However, in some cases neurological deterioration occurred after TCA (imipramine) treatment.⁵⁵

Parkinson's disease (PD) recommendations suggest the initial use of psychotherapy for mild depression, followed by the TCA with the lowest anticholinergic effects (nortriptyline or desipramine) or an SNRI (venlafaxine or duloxetine), and less frequently SSRIs. ECT may be used for severe refractory depression.¹⁹ Some authors recommend the use of SSRIs for depression in PD (especially sertraline); however, SSRIs showed less efficacy in comparison with select TCAs in some studies.^{22,23} There are no randomized trials

evaluating the efficacy and safety of antidepressant treatment in WD; therefore the clinician must make the choice of treatment, and SSRIs appear to be a reasonable choice as a first-line treatment.²³ It is also important to avoid antidepressant drugs with a higher risk of liver injury, such as iproniazid, phenelzine, imipramine, amitriptyline, duloxetine, bupropion or agomelatine when choosing a treatment for WD patients.^{1,56}

Bipolar disorder has been reported more frequently in WD than in the healthy age- and gender-matched population, at 14–18%.⁵⁴ Unfortunately, studies on the prevalence and incidence of bipolar disorder among WD patients rarely consider the differentiation between bipolar mania/hypomania and symptoms related to brain damage. Emotional lability, irritability and aggression, shallow cheerfulness, euphoria, social disinhibition, hypersexuality, lack of criticism and deficits in planning and anticipating social consequences can all be due to lesions to the frontal lobe or its associated pathways.⁵⁴

The effects of various mood stabilizers have been reported for cases of manic/hypomanic syndrome over the course of bipolar disorder in WD, including lithium, antiepileptic drugs (carbamazepine, oxcarbazepine, valproate, lamotrigine, gabapentin) and various antipsychotic agents including haloperidol, promethazine, olanzapine, risperidone, quetiapine and aripiprazole in cases of severe mania.^{12,14,33,34,51,54} Positive treatment outcomes are generally reported; however, neurological deterioration occurred in some cases of antipsychotic treatment, especially with 'classical' first-generation agents.⁵⁷ This could correspond with PD guidelines for the treatment of psychotic symptoms, which recommend using clozapine or quetiapine only, due to their lower risk of deterioration of parkinsonism.¹⁹ Another potential drug for use in WD is olanzapine. It is one of the most effective anti-manic drugs and is associated with a much lower risk of inducing extrapyramidal symptoms relative to haloperidol and other first-generation antipsychotics. Available case reports indicate good efficacy and safety for its use in the treatment of the psychiatric symptoms of WD.¹²

Mood disorders, especially depression, are frequently under-recognized in patients with chronic neurological illnesses.¹² We recommend depression screening for all WD patients, and those with diagnosed mood disorders should receive treatment. Monitoring symptom severity with an

appropriate scale (such as the Hamilton Depression Scale or Montgomery–Asperg Depression Rating Scale) might be clinically valuable.

Psychosis in WD and its treatment

Wilson reported psychosis in 2 of the 12 patients described in his initial monograph.³ Currently, epidemiological studies suggest that psychosis in WD occurs rarely and is not more frequent than in the general population; however, it does occur more often in patients with a neurological WD manifestation.^{10,12,14,46,51} No specific clinical manifestations of psychosis in WD have been described, and patients typically carried a diagnosis of schizophrenia, schizoaffective, and/or delusional disorders.

Psychotic symptoms occurring as the first manifestation of WD could present both diagnostic and therapeutic challenges.^{58–62} Since approximately 3% of first-episode psychosis cases may be due to ‘organic’ causes, some diagnostic guidelines suggest screening for WD in first-episode psychotic patients. However, such procedures are not routine, and serum ceruloplasmin level, often performed as a single test, is not sufficiently sensitive.^{12,63,64}

From the clinical point of view, the pharmacological treatment of WD patients with symptoms of psychosis requires caution for two reasons, the risk of neurological deterioration, and the risk of hepatic injury due to existing hepatic impairment.^{12,57} Therefore, agents with low risk of extrapyramidal symptoms as well as low hepatic risk are recommended as the first-line treatment for psychosis in WD patients. Clinical experience and PD studies suggest clozapine or quetiapine as safe options.^{15,59,65,66} However, clozapine treatment should be reserved for the most severe and treatment-resistant cases due to increased risk of leucopenia. WD patients are known to be more vulnerable to leucopenia, as it may also be caused by interactions with chelation treatment, and it has been observed in patients with liver cirrhosis.¹ Regular blood analysis is mandatory in these cases.¹ Clozapine can also lead to dose-related seizures, which is an important safety issue in this context, since 6–8% of WD patients also suffer from epilepsy.⁶²

Aripiprazole has very good safety profile, but results are conflicting in case studies of its use for WD treatment.^{62,66} Olanzapine and quetiapine

are antipsychotics with moderate risk when used in patients with liver injury.⁵⁶ Amisulpride and sulpiride might be interesting options because these benzamides are not metabolized in the liver and are assessed to carry a low risk of extrapyramidal symptoms, especially at lower doses.⁵⁶ Other antipsychotics with positive effects on psychosis in WD include risperidone, haloperidol, perphenazine, thioridazine and chlorpromazine; however, neurological deterioration, including neuroleptic malignant syndrome, were more frequently reported when using these drugs, especially with typical antipsychotics.^{67,68} Long-acting antipsychotics should be used in patients with WD only with great caution.^{14,15}

Behavioral and other psychiatric disorders

Behavioral and personality disorders are frequent psychiatric symptoms of WD. They are reported to occur in 46–71% of WD patients, and the most common manifestations are irritability, aggression and antisocial behavior.^{8,10,41} Portala and colleagues³⁰ were the first to describe personality changes in WD patients using the Karolinska Scale of Personality (KSP). A comparison of a group of 25 WD patients with a healthy control group showed that WD patients scored significantly higher on both aggressive hostility and psychic anxiety scales. The authors also noticed that specific mutations of the *ATP7B* gene correlated with specific personality traits.

Behavioral and personality disturbances could lead to serious social problems, including family difficulties (divorces, unemployment, or even criminal activity), as well as difficulties receiving medical care, including treatment, diagnosis, and rehabilitation (issues include verbal aggression and non-compliance with anti-copper treatment as well as other medical recommendations).^{10,69} Behavioral and personality problems can negatively affect treatment outcomes in WD, so it is important to assess them at the beginning of treatment and monitor them.¹⁰ However, there are currently no data informing the treatment of these disturbances in WD patients.¹

Some recommendations could be made based on general psychiatry recommendations, and those for behavioral disturbances, especially aggression, in HD and other BG disorders.¹⁸ Behavioral therapy could be applied, depending on the severity of the symptoms and their impact on the daily functioning of the affected patients. SSRIs

(citalopram, escitalopram and sertraline) can reduce irritability and could be a relatively safe first-line option for pharmacological treatment. Antiepileptic medications may also have some anti-aggressive and mood stabilizing effects, and promising results have been obtained with carbamazepine, lamotrigine, gabapentin, oxcarbamazepine and valproate.¹⁸ It should be stressed that of the antiepileptic drugs, gabapentin and levetiracetam are considered to be mostly safe for the liver as they are excreted by the kidneys, but there are few studies documenting their efficacy in personality disorders. Antipsychotic drugs can be used in cases with severe symptoms, but they may pose an increased risk for extrapyramidal symptoms and neuroleptic malignant syndrome in WD patients.⁶⁷ Therefore, their use should be restricted to the shortest effective time course with the lowest effective dosages, and preference should be given to agents with the lowest risk of extrapyramidal symptoms (like clozapine or quetiapine).^{19,59,65} Benzodiazepines are a safe option for short-term acute management of aggression in WD patients, but their long-term use can be problematic.^{21,22} Some data also indicate the efficacy of beta-blockers (propranolol) for the treatment of irritability in HD.¹⁸ Propranolol could be an interesting option in WD due to its multimodal action that includes efficacy for both neurologic (tremor) and liver symptoms (portal hypertension).^{1,62}

The symptoms and diagnosis of an illness as serious as WD can be a major stressor, often leading to significant life changes, difficulties with normal functioning, and can lead to a decline in social and material status.⁶⁹ Many patients with WD suffer from various forms of adjustment disorders, manifesting as a mixture of anxiety, depression, worry, insomnia and tension, but also irritability, anger and conduct disorders.¹⁰ Simple interventions such as psychoeducation, supportive psychotherapy, cognitive-behavioral therapy (CBT) and support groups might help to reduce anxiety and tension, and facilitate the development of good coping strategies to adapt to the new life situation of chronic illness.¹⁸ Unfortunately, currently there are no data documenting the effectiveness of these specific strategies for WD.¹ More severe forms of adjustment disorder might need pharmacological treatment with SSRI antidepressants as a first-line option.^{18,22}

A few other psychiatric conditions including catatonia, anorexia nervosa, bulimia, obsessive-compulsive disorder and ADHD have also been

reported in WD.^{28,29,70,71} In most described cases, psychiatric manifestations lead to a delay in WD diagnosis. However, an improvement was typically observed after the correct diagnosis of WD, anti-copper treatment introduction and psychiatric treatment (lorazepam followed by ECT in catatonia; SSRI with behavioral therapy in obsessive-compulsive disorder).^{12,14}

In summary, there is a wide spectrum of psychiatric symptoms observed in WD, leading to the conclusion that WD should be included in differential diagnosis, especially in young adults presenting with the first episode of psychiatric symptoms,¹² and WD should be suspected in all young adult psychiatric patients presenting with extrapyramidal and/or hepatic symptoms.^{12,13,62}

Cognitive deficits

Cognitive deficits are reported in approximately 25% of WD patients, often in patients with neurological symptoms.¹⁰ The cognitive domains affected include attention, visuospatial perception and reasoning, learning and memory, and verbal and abstract reasoning.³⁵⁻³⁹ Generally, cognitive deficits are mild and potentially reversible at disease onset, but can deteriorate during the progression of the disease, and some patients may eventually receive the diagnosis of mild cognitive disorder or even dementia.³⁵ We note that separate diagnostic categories exist in ICD-10 classification for other BG diseases, such as dementia in PD and dementia in HD.

In contrast to neurodegenerative dementias, intellectual deficits presenting in WD patients are secondary to metabolic changes, similarly to those occurring in hepatic encephalopathy or manganism, and are potentially reversible with anti-copper treatment.^{35,38} The most frequent deficits are found in the executive domain, while verbal intelligence and episodic memory are preserved.³⁹ WD patients may also have a slow processing speed and mild impairment in all cognitive domains, particularly in working memory, attention and abstract thinking. These cognitive deficits are likely to be associated with lesions in the cortico-striatal pathways, and correlate with the global severity of MRI abnormalities.^{36,37,39,72,73}

There are currently no pharmacological agents used for cognitive disturbances in WD, and there are no published studies describing the

efficacy and safety of cholinesterase inhibitors or memantine in WD.¹ The direct effect of toxic copper has been postulated in the etiology of cognitive deficits in WD. The pathological effect of toxic ‘free copper’ on neurons and cognitive function was demonstrated in AD, and higher levels of ‘free copper’ correlated with an unfavorable evolution of cognitive deficits.⁷⁴ This may be why the only currently available pharmacological option for cognitive deficits in WD is anti-copper treatment.¹

Discussion

While WD is a metabolic disorder potentially treatable with anti-copper agents,^{1,5,6} there are many problems related to the treatment of clinical symptoms outside of hepatic ones. The psychiatric symptoms of WD are highly prevalent and among the biggest challenges in WD management for several reasons.^{4,27,55,57,67,68} First, because the early diagnosis of WD in patients with initial psychiatric symptoms is difficult,^{12,13,70,75} and second, because there are no guidelines for the treatment of psychiatric symptoms in WD that take the specificity of this disorder into account.¹

The psychiatric manifestations of WD may have a negative impact on the recovery or even survival of the affected patients.^{1,4} Delays in correct diagnosis, negative impacts on compliance with anti-copper drugs, as well as adverse reactions to drugs related to psychiatric treatment (e.g. neurological worsening, neuroleptic malignant syndrome, drug-related liver failure) are all important factors.^{9,57,73,76,77} In cases presenting with initial hepatic symptoms, the mean delay of WD diagnosis is 6 months; in cases with initial neurological symptoms it is 18 months; and in the case of psychiatric manifestation it is 26 months, although a delay of up to 12 years has been reported.¹

The determination of ceruloplasmin concentration has been proposed as an initial test for WD; however, it appeared to have low sensitivity as a sole assessment.^{63,64} Currently, in cases of first psychiatric episode (especially in young adults), baseline liver tests, an interview including history of hepatic disorders, detailed family history (including liver, neurological and psychiatric disorders including WD), physical examination (including general, neurological and ophthalmological assessment) and brain magnetic resonance imaging are recommended in order to exclude

WD before beginning psychiatric pharmacological treatment.^{13–15} In cases with abnormal results, international WD diagnostic criteria such as the Ferenci score (Table 2) should be used to confirm the WD diagnosis.¹

The main goal of this review is to recommend classes of drugs as potentially safe and effective for the treatment of the most prevalent psychiatric symptoms of WD (Table 3). These treatments directed at symptom management should be added to the anti-copper treatment that forms the basis for recovery from WD symptoms and which can lead to global improvement of WD symptoms.^{1,78} The limitation of this review is the fact that there were no clinical trials performed examining psychiatric treatment for WD, and our recommendations are based on available data, which come primarily from case studies and from general recommendations for other BG disorders.

Another issue to be discussed in the context of the treatment of WD symptoms is liver transplantation (LT). Such a procedure may correct the genetic defect related to ATP-ase7B in the liver, which leads to the normalization of copper metabolism.¹ There are published case reports describing the recovery of neurological symptoms as well as psychosis following LT.^{79–82} However, two analyses of WD patients who received LT (Medici and colleagues⁸³ and Guillaud and colleagues⁸⁴) showed that the presence of neuropsychiatric symptoms in WD patients is associated with a poor outcome following LT. Therefore, according to international recommendations, LT is currently reserved for hepatic indications only.¹

Conclusion

Psychiatric symptoms are common at every stage of WD and there is often an extremely long delay in WD diagnosis for patients with psychiatric symptoms. WD should therefore be included in differential psychiatric diagnosis, especially in young adults presenting with the first psychiatric episode. Due to the frequently complex clinical presentation of WD that can include hepatic, neurological and psychiatric symptoms, the illness should be treated by a multidisciplinary team with a complex assessment of the various aspects of WD.^{1,62,85–87} Basic anti-copper treatment typically leads to an improvement of hepatic, neurological and psychiatric symptoms. When specific psychiatric treatment is needed, potentially hepatotoxic drugs should be avoided.

Table 2. The scoring system (Ferenci score) for the diagnosis of Wilson's disease developed at the 8th International Meeting on Wilson's Disease and Menkes Diseases, Leipzig 2002.

K-F rings	Present (2 points)	Absent (0 points)	
Neuropsychiatric symptoms suggest WD (or typical brain MRI)	Yes (2 points)	No (0 points)	
Coombs negative hemolytic anemia	Yes (1 point)	No (0 points)	
24 h urinary copper excretion (in the absence of acute hepatitis)	Normal (0 points)	1–2 × ULN (1 point)	>2 × ULN, or normal, but >5 × ULN after challenge with 2 × 0.5 g D-penicillamine (2 points)
Liver copper quantitative	Normal (–1 point)	<5 × ULN (1 point)	>5 × ULN (2 points)
Rhodanine-positive hepatocytes (only in case of lack of Cu quantitative assessment)	Absent (0 points)	Present (1 point)	
Serum ceruloplasmin (nephelometric assay, normal >20 mg/dL)	Normal (0 points)	10–20 mg/dL (1 point)	<10 mg/dL (2 points)
Mutation analysis	Disease causing mutations on both chromosomes (4 points)	Disease causing mutations on one chromosome (1 point)	No mutation detected (0 points)

Assessment of the WD diagnosis score:
 ≥4 points: diagnosis of WD highly likely.
 2–3 points: diagnosis of WD probable, more investigations needed.
 0–1 point: diagnosis of WD unlikely.
 MRI, magnetic resonance imaging; ULN, upper limit of normal.

Table 3. Pharmacological and non-pharmacological treatment options for psychiatric symptoms in patients with WD.

WD psychiatric symptoms	Therapeutic interventions		
	Preferred options	Alternative options	Avoid or special precaution needed
Mood disturbances depression	SSRI: Citalopram 20–40 mg Escitalopram 10–20 mg Sertraline 50–200 mg	Selected TCA nortriptyline 50–150 mg Desipramine 50–150 mg SNRI Venlafaxine 75–225 mg SSRI Paroxetine 20–60 mg Mirtazapine 15–45 mg ECT	Agomelatine Bupropion Amitriptyline, Duloxetine Imipramine Iproniazid Phenelzine (Higher risk of liver injury)
Mania (bipolar disorder)	Mood stabilizers: lithium carbonate (with target serum level 0.6–1.0 mmol/L)	Antiepileptic drugs: carbamazepine; lamotrigine (for depression)	Valproate is effective but caution is needed because of risk of hepatotoxicity

Table 3. (Continued)

WD psychiatric symptoms	Therapeutic interventions		
	Preferred options	Alternative options	Avoid or special precaution needed
	Antiepileptic drugs: valproate 500–1000 mg/day Atypical antipsychotics: olanzapine 5–20 mg; quetiapine 300–800 mg	Atypical antipsychotics: aripiprazole 10–30 mg	Lithium treatment should be carefully monitored Avoid haloperidol and high-potency antidopaminergic agents
Psychosis	Atypical antipsychotics: olanzapine 10–20 mg; quetiapine 300–800 mg; aripiprazole 15–30 mg	Amisulpride 200–800 mg Sulpiride 200–800 mg	Clozapine only for treatment-resistant cases (leukopenia and seizures risk) Avoid haloperidol and high-potency antidopaminergic agents Avoid long-acting antipsychotics
Catatonia	BZD (lorazepam) ECT	Olanzapine Quetiapine	Avoid haloperidol and high-potency antidopaminergic agents Very high risk of NMS
Obsessive-convulsive disorder	SSRI: escitalopram 10–20 mg; sertraline 50–200 mg	SSRI: fluvoxamine 150–250 mg; paroxetine (20–60 mg) CBT (exposure and response prevention)	TCA Clomipramine (50–250 mg)
Behavioral disturbances (treatment strategy primarily depends on disturbance severity – details in main text)	Behavioral therapy SSRI: citalopram, escitalopram, sertraline) Antiepileptic drugs: carbamazepine, lamotrigine, gabapentin, pregabalin BZD short term: lorazepam, oxazepam, temazepam Adrenergic beta-blockers (propranolol 20–60 mg)	Atypical antipsychotics: quetiapine 50–300 mg; tiapride 50–200 mg	Avoid haloperidol and high-potency antidopaminergic agents Avoid long-acting benzodiazepines Valproate – caution is needed because of risk of hepatotoxicity High dose of propranolol – higher risk of hepatotoxicity
Cognitive deficits	Neuropsychological training		Avoid agents that may worsen cognition – BZD, strong anticholinergic; avoid sedation

BZD, benzodiazepines; CBT, cognitive-behavioral therapy; ECT, electroconvulsive therapy; NMS, neuroleptic malignant syndrome; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; WD, Wilson's disease.

More research is necessary to inform clinicians about the efficacy and safety of psychotropic agents for WD patients, and about how long psychiatric

treatment should be administered, when it can be safely discontinued and in which cases long-term maintenance treatment is necessary. There is also a

need to perform clinical studies in WD, with detailed psychiatric assessment scales (e.g. MINI International Neuropsychiatric Interview used in the WTX101-201 study),⁸⁸ which will be helpful to describe the psychiatric manifestation of WD as well as show us the effectiveness of different treatment regimens in psychiatric WD. Additionally, in view of the lack of dedicated scales to assess the psychiatric symptoms of WD, there is also a need to elaborate such an evaluation scale and to incorporate it into the global assessment of WD in order to plan and perform adequate psychiatric treatment.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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