



# Investigation and management of Wilson's disease: a practical guide from the British Association for the Study of the Liver

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Wilson's disease is an autosomal-recessive disorder of copper metabolism with hepatic, neurological, psychiatric, ophthalmological, haematological, renal, and rheumatological manifestations. Making a diagnosis can be challenging given that no single test can confirm or exclude the disease, and diagnostic delays are common. Treatment protocols vary and adverse effects, including paradoxical neurological worsening, can occur. In this Review, we provide a practical guide to the diagnosis of Wilson's disease. We include recommendations on indications for testing, how to interpret results, and when additional investigations are required. We also cover treatment initiation, ideally under the guidance of a specialist centre for Wilson's disease, and the principles behind long-term management. This guidance was developed by a multidisciplinary group of Wilson's disease experts formed through the British Association for the Study of the Liver. The guidance has been endorsed by the British Society of Gastroenterology and approved by the Association of British Neurologists.

## Introduction

Wilson's disease is an autosomal recessive disorder of copper metabolism with an estimated disease prevalence of 2 per 100 000 people in the UK.<sup>1</sup> *ATP7B* mutations lead to impaired biliary excretion and subsequent accumulation of copper in multiple organ systems. Most patients present between the ages of 3 years and 40 years with liver disease, a movement disorder, or psychiatric features. However, ophthalmological, haematological, renal, and rheumatological manifestations can also occur,<sup>2,3</sup> and presentations in older adults, including individuals in their 70s, are described.<sup>4,5</sup> Clinical presentations are thus highly variable, often mimicking more common diseases, and diagnoses are frequently missed or delayed.<sup>6</sup> Although routine investigations can be suggestive of Wilson's disease, specialised tests are required to confirm the diagnosis.

In this Review, we clarify the indications for specific investigations and how they should be interpreted. We also discuss common pitfalls in diagnosis and management and make consensus recommendations for both paediatric and adult patients. Compared with previous guidelines, this Review offers a more practical guide to the investigation and management of Wilson's disease for the non-expert that includes advice on how to screen for neurological involvement at the bedside, which investigations are indicated in specific clinical scenarios, how these should be prioritised, and when and how to proceed with initiating treatment, in addition to incorporating recent changes in clinical practice over the past decade.<sup>7-10</sup>

## Data collection

### Background and methods

This Review was commissioned by the British Association for the Study of the Liver Rare Diseases Special Interest Group to provide advice for general physicians on the initial investigation and management of Wilson's disease

and to promote interdisciplinary working. The working party was chaired by OB and included experts in adult hepatology (TM, AA, GA, JD, and WG), paediatric hepatology (AS, SV, AD, and DK), adult neurology (SS, TTW, and OB), genetics (AM), and clinical chemistry (GTG), alongside patient representation (VW). The major subject areas were agreed by the working party and allocated to individuals responsible for searching the literature and synthesising the evidence (SS, TM, AS, and SV). The writing group (SS, TM, AS, SV, GA, AD, GTG, DK, TTW, WG, and OB) then had a series of six interval virtual meetings to evaluate the evidence and agree on a set of provisional consensus recommendations. The guidance document and recommendations were then circulated to the entire British Association for the Study of the Liver Rare Diseases Special Interest Group, and expert members of the British Society of Gastroenterology, Association of British Neurologists, and Wilson's Disease Support Group UK. After addressing reviewer comments, all societies formally approved the guidance and recommendations. The level of supporting evidence for the recommendations was assessed using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.<sup>11</sup> Each recommendation was awarded a score ranging from 1 to 5 based on the relevant research question in the Oxford Centre for Evidence-Based Medicine classification, with a score of 1 indicating the strongest level of evidence. This process took place over a total of 10 months between January, 2021, and October, 2021.

### Search strategy and selection criteria

The published literature (prior to May 1, 2021) was searched using PubMed, Cochrane, and Google Scholar. Studies were identified using keywords, including "Wilson's disease" and "Wilson disease". These searches were combined with the set operator "AND" with additional terms including "chelation", "penicillamine", "trientine",

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“zinc”, “cirrhosis”, “movement disorder”, and “acute liver failure” to identify relevant studies. Additionally, abstracts from conference proceedings from the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases (2017–20) were manually searched to identify potentially eligible studies in abstract form. Reference lists from identified articles were also assessed for relevance. ClinicalTrials.gov was searched using the terms “Wilson’s disease” and “Wilson disease” to screen for relevant ongoing interventional studies. The final reference list was generated on the basis of applicability to the broad scope of this guidance document.

## Findings and guidelines

### Clinical presentation and indications for testing

The most striking reason to suspect Wilson’s disease is the combination of liver disease with a movement disorder or psychiatric features.<sup>12</sup> Patients with hepatic disease tend to present at a younger age than those with neurological manifestations.<sup>6,13</sup> Irrespective of the initial presentation, a family history of liver disease or a movement disorder in a sibling should immediately raise suspicion for Wilson’s disease, noting that presentation can vary considerably within families.<sup>14</sup>

We advocate for a pragmatic approach to the diagnosis of Wilson’s disease in which routine investigations (ie, a full blood count, liver biochemistry, coagulation profile and serum caeruloplasmin) are performed in individuals in whom there is a lower index of suspicion, and a wider screen (ie, a 24-h urine collection and slit lamp examination) reserved for individuals with additional clinical features suggestive of Wilson’s disease. Several additional tests might be required in specific circumstances. These categories of investigations are presented in figure 1, which provides an overview of the major learning points and consensus recommendations in this guidance document.

#### Patients presenting with suspected liver disease

Virtually all patterns of liver disease have been described in Wilson’s disease in both paediatric and adult populations. These patterns include asymptomatic derangements in liver biochemistry, hepatic steatosis on imaging, hepatomegaly, acute hepatitis, cirrhosis, and acute liver failure.<sup>15–19</sup> When faced with any of these clinical presentations, Wilson’s disease should form part of the differential diagnosis and routine investigations should be arranged (recommendation 1.1; table 1). The index of suspicion should be higher in children than adults and a wider screen should be performed at initial presentation to a paediatrician (recommendation 1.2; table 1). In adults, most presentations with liver disease will be secondary to more common causes such as alcohol, non-alcoholic fatty liver disease, and viral hepatitis. Therefore, a wider screen should be performed when an alternative cause for liver disease cannot be identified (recommendation 1.3; table 1) or there are additional features of Wilson’s disease such as

a movement disorder or unexplained haemolytic anaemia, (recommendation 1.4; table 1) or serum caeruloplasmin is low.

Wilson’s disease can mimic or co-exist with other liver pathology. Hepatic steatosis identified on imaging or biopsy is common in Wilson’s disease and can be misattributed to alcohol or non-alcoholic steatohepatitis. Similarly, histological features of Wilson’s disease on liver biopsy can resemble autoimmune hepatitis and clinicians should keep an open mind for Wilson’s disease in individuals diagnosed with autoimmune hepatitis who do not respond to immunosuppressive medication.<sup>20</sup> Left untreated, Wilson’s disease progresses to cirrhosis, which is present in 25–54% of patients at diagnosis and can ultimately become decompensated with jaundice, ascites, variceal haemorrhage, hepatic encephalopathy, and susceptibility to infection.<sup>21–24</sup>

#### Acute liver failure

Up to 20% of patients with Wilson’s disease with hepatic presentations have acute hepatic Wilson’s disease, formerly fulminant Wilson’s disease,<sup>25</sup> with a higher frequency in paediatric cohorts than adult cohorts.<sup>26</sup> This severe acute liver injury can rapidly progress to acute liver failure, defined in adults by the presence of jaundice, coagulopathy, and encephalopathy.<sup>27,28</sup> Coagulopathy is an independent risk factor for death in children in whom mental status is more difficult to assess. Paediatric acute liver failure is therefore defined as an acute liver injury with a prothrombin time of more than 15 s or international normalised ratio of more than 1.5 not corrected by vitamin K in the presence of encephalopathy or a prothrombin time of more than 20 s, or international normalised ratio of more than 2.0 regardless of the presence or absence of encephalopathy.<sup>29</sup> Definitions of acute liver failure and paediatric acute liver failure traditionally require the absence of chronic liver disease; however, an exception is made in Wilson’s disease in which most patients will have underlying cirrhosis at initial presentation.<sup>30</sup>

The typical presentation is a young patient (aged 5–40 years) presenting with moderately elevated aminotransferases and a high bilirubin to alkaline phosphatase ratio who develops a Coombs-negative haemolytic anaemia and encephalopathy. Acute hepatic Wilson’s disease is more common in female than male patients (4:1) and often presents de novo and without warning, although there could be a concurrent viral trigger.<sup>26</sup> It could also occur in patients with an established diagnosis of Wilson’s disease with non-adherence to medication.

#### Patients presenting with neurological symptoms

Slurred speech is the most common neurological symptom of Wilson’s disease and is reported in 52% of children and 74–91% of adults with neurological presentations.<sup>6,31</sup> A postural tremor of the upper limbs is

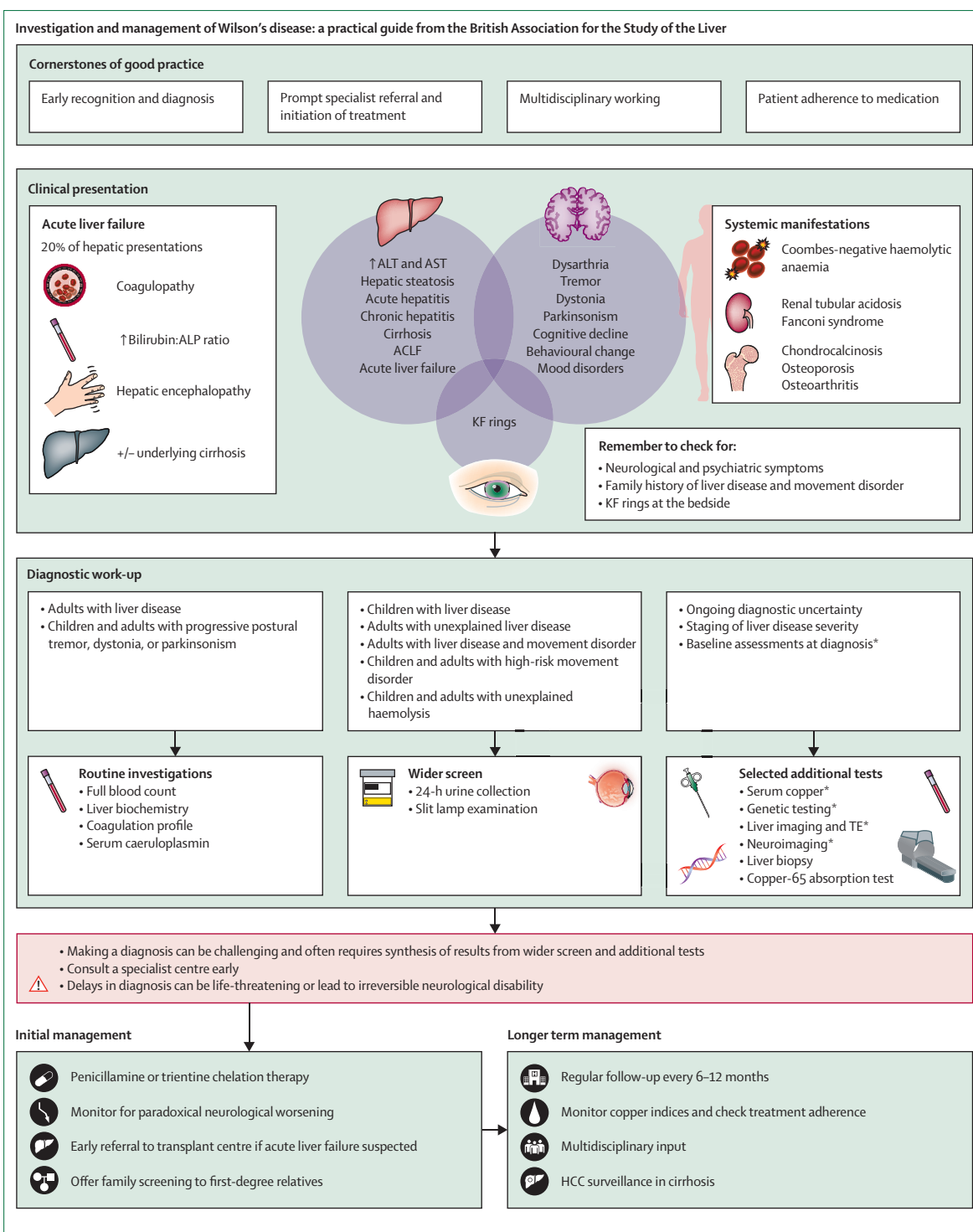


Figure 1: Investigation and management of Wilson's disease

\*Tests which should be offered to all patients at diagnosis.

ACLF=acute-on-chronic liver failure. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. HCC=hepatocellular carcinoma.

KF=Kayser-Fleischer. RTA=renal tubular acidosis. TE=transient elastography.

|  | Level of evidence |
|--|-------------------|
| <b>Indications for testing</b>   |                   |
| 1.1 All adults presenting with liver disease should have routine investigations for Wilson's disease   | 3                 |
| 1.2 All children presenting with liver disease should have routine investigations and a wider screen for Wilson's disease  | 3                 |
| 1.3 All adults with unexplained liver disease despite investigation with laboratory tests, liver imaging, and histology should have a wider screen for Wilson's disease  | 3                 |
| 1.4 All adults with liver disease in combination with a movement disorder or unexplained haemolytic anaemia should have routine investigations and a wider screen for Wilson's disease   | 4                 |
| 1.5 All patients between the age of 5 years and 50 years who develop a progressive postural tremor, dystonia, or parkinsonism, except patients with isolated cervical dystonia or blepharospasm, should have routine investigations for Wilson's disease   | 4                 |
| 1.6 All patients who develop a mixed movement disorder with any red flags (subacute onset or progression, early bulbar involvement, executive dysfunction, behavioural or personality changes, or suspected liver disease) should have routine investigations and a wider screen for Wilson's disease, in addition to neuroimaging | 4                 |
| 1.7 All patients with an unexplained Coombs-negative haemolytic anaemia should have routine investigations and a wider screen for Wilson's disease   | 4                 |
| <b>Interpretation of initial investigations</b>  |                   |
| 2.1 Serum caeruloplasmin <0.10 g/L is highly suggestive of Wilson's disease but a wider screen for Wilson's disease is usually required to make a diagnosis  | 2                 |
| 2.2 Serum caeruloplasmin 0.10–0.20 g/L has numerous causes and a wider screen for Wilson's disease is indicated  | 2                 |
| 2.3 Serum caeruloplasmin >0.20 g/L does not exclude a diagnosis of Wilson's disease but reduces the likelihood of it   | 2                 |
| 2.4 Patients should be offered written instructions for 24-h urine collections and provided with non-acid-washed containers  | 3                 |
| 2.5 Copper output >0.64 µmol/24 h (40 µg/24 h) is suggestive of Wilson's disease but further investigations are required to make a diagnosis   | 2                 |
| 2.6 The presence of Kayser-Fleischer rings on slit lamp examination is highly suggestive of Wilson's disease   | 2                 |
| 2.7 Initial investigations should be performed as soon as possible given the risk of hepatic and neurological deterioration  | 4                 |
| 2.8 Patients suspected to have Wilson's disease should be urgently discussed with a specialist centre  | 4                 |
| <b>Additional investigations</b>   |                   |
| 3.1 Serum copper should not routinely be used alone to confirm or exclude a diagnosis of Wilson's disease  | 3                 |
| 3.2 Clinicians should not delay initiation of treatment while serum copper test results are pending  | 4                 |
| 3.3 Genetic testing is required in all patients suspected to have Wilson's disease on clinical and biochemical grounds but should not delay the initiation of treatment  | 3                 |
| 3.4 All patients with suspected Wilson's disease should have a liver ultrasound scan irrespective of their clinical presentation   | 2                 |
| 3.5 Liver stiffness measurement by transient elastography should be performed in all adults without overt cirrhosis at the point of Wilson's disease diagnosis   | 2                 |
| 3.6 Wilson's disease should be considered in patients with an unexplained movement disorder and signal abnormalities in basal ganglia, thalamus, or brainstem  | 3                 |
| 3.7 MRI brain scan is indicated in any patient with suspected Wilson's disease who has neurological or psychiatric manifestations  | 2                 |
| 3.8 All patients with a confirmed diagnosis of Wilson's disease should have an MRI brain scan, irrespective of their initial presentation  | 2                 |
| 3.9 A liver biopsy with hepatic dry weight parenchymal copper could help with the diagnosis of Wilson's disease when other non-invasive tests have proved inconclusive   | 2                 |
| 3.10 In the absence of cholestatic liver disease, a hepatic parenchymal copper content >209 µg/g dry weight tissue is highly suggestive of Wilson's disease  | 2                 |
| 3.11 A liver biopsy could be considered in patients with a confirmed diagnosis of Wilson's disease when there is clinical uncertainty about the presence or absence of cirrhosis   | 2                 |
| 3.12 Liver biopsy is not indicated in patients with a confirmed diagnosis of Wilson's disease who have no evidence of liver involvement  | 4                 |
| 3.13 A copper-65 test can be performed in specialist centres when other tests are inconclusive and clinical suspicion remains  | 3                 |

(Table 1 continues on next page)

the most common movement disorder. The tremor is usually irregular or jerky and can easily be examined by asking patients to hold out their arms. However, other movement disorders including dystonia, parkinsonism, ataxia, and, less commonly, chorea, can occur.<sup>6,31,32</sup> A glossary for these terms is provided in the appendix (p 1). Patients could refer to shaking, clumsiness, or loss of balance. Handwriting is often affected and should be specifically assessed, particularly in children.<sup>6</sup> Some

patients also have a characteristic grimacing facial expression (risus sardonicus) and seizures occur in around 10% of children with neurological presentations.<sup>6,33</sup>

Several clinical features can help differentiate movement disorders in Wilson's disease from other conditions. Firstly, although symptoms are often chronic and slowly progressive, some patients with Wilson's disease have a subacute onset with progression over months; this is unusual in other movement disorders and

See Online for appendix

|  | Level of evidence |
|--|-------------------|
| (Continued from previous page)   |                   |
| <b>Initial management</b>  |                   |
| 4.1 All children with paediatric acute liver failure or decompensated liver disease should be urgently referred to a paediatric liver transplant centre  | 2                 |
| 4.2 Adults with acute liver function should be urgently referred to a liver transplant centre  | 2                 |
| 4.3 Liver transplantation is indicated in children who have decompensated liver disease with encephalopathy  | 2                 |
| 4.4 Liver transplantation should be considered in all adults with acute liver failure  | 2                 |
| 4.5 The new Wilson index should be used for prognosis and to facilitate decision making for liver transplantation in children  | 3                 |
| 4.6 Penicillamine monotherapy is the first-line treatment for children and adults in the UK and should be introduced in consultation with a specialist centre for Wilson's disease   | 3                 |
| 4.7 Trientine dihydrochloride or tetrahydrochloride can be used in children and adults intolerant to penicillamine or at increased risk of adverse effects   | 3                 |
| 4.8 Penicillamine should be introduced gradually with dose increments of 125–250 mg per week in children   | 4                 |
| 4.9 Penicillamine should be introduced gradually with dose increments of 125–250 mg per week in adults with neurological or psychiatric symptoms   | 4                 |
| 4.10 Penicillamine can be introduced more quickly in adults presenting with decompensated liver disease in the absence of neurological symptoms or neuroimaging abnormalities  | 4                 |
| 4.11 A full blood count, liver function tests, renal profile, and urine dipstick should be performed to monitor for adverse effects before starting penicillamine, after 1 week of treatment and then every 2 weeks for 3 months   | 4                 |
| 4.12 Zinc salts are considered a third-line treatment for adults in the UK and should only be initiated by specialist centres; they are not recommended as monotherapy in patients with cirrhosis unless other treatments are unavailable or contraindicated               | 3                 |
| 4.13 We cannot make a strong recommendation for the use of zinc salts in children because of inadequate data; zinc salts have been used by paediatric hepatologists in children identified through family screening, or as maintenance therapy with or without chelators   | NA                |
| 4.14 Dietary copper intake should be restricted in the first year of treatment; decisions to continue this after 1 year should consider response to treatment, and adherence and impact on quality of life   | 4                 |
| 4.15 Patients with neurological symptoms should have regular follow up with a movement disorders specialist for a minimum of 12 months after treatment initiation  | 4                 |
| 4.16 24-h urinary copper output while continuing medication (on treatment) should be measured within the first 2 months to confirm an adequate copper excretion  | 4                 |
| <b>Long-term management</b>  |                   |
| 5.1 24-h urinary copper output while continuing medications (on treatment) should be 3–8 $\mu\text{mol}/24\text{ h}$ (200–500 $\mu\text{g}/24\text{ h}$ ) with chelating agents and 0.5–1.2 $\mu\text{mol}/24\text{ h}$ (30–75 $\mu\text{g}/24\text{ h}$ ) with zinc salts | 4                 |
| 5.2 24-h urinary copper output after 48 h of treatment cessation (off treatment) should be 0.2–0.6 $\mu\text{mol}/24\text{ h}$ (12–40 $\mu\text{g}/24\text{ h}$ ) for patients treated with chelating agents   | 4                 |
| 5.3 Non-caeruloplasmin-bound copper should be <2.4 $\mu\text{mol}/\text{L}$ (15 $\mu\text{g}/\text{dL}$ )  | 4                 |
| 5.4 Hepatocellular carcinoma screening should be considered in patients with cirrhosis using 6-monthly ultrasound  | 4                 |
| 5.5 Chelation therapy should be continued throughout pregnancy   | 3                 |
| 5.6 Women on chelation therapy should not be advised against breastfeeding   | 4                 |
| <b>Family screening</b>  |                   |
| 6.1 Clinical assessment, routine investigations, and genetic screening should be offered to all first-degree relatives of patients diagnosed with Wilson's disease   | 2                 |
| 6.2 Treatment of asymptomatic patients should only be initiated by specialist centres  | 4                 |
| NA=not applicable.   |                   |
| <b>Table 1: Consensus recommendations for the investigation and management of Wilson's disease</b>   |                   |

should prompt urgent investigation. Secondly, movement disorders in Wilson's disease often occur in combination as mixed movement disorders with dystonic tremor or dystonia–parkinsonism syndromes. Thirdly, early bulbar involvement, which could include dysphagia or drooling in addition to dysarthria, is common in Wilson's disease but unusual in other causes of movement disorders.

#### Neuropsychiatric features

Executive function could be impaired but this can be subtle and easily missed in a brief consultation.<sup>34–36</sup> Processing

speed, memory, and social cognition can also be affected.<sup>37</sup> Asking about difficulties at school, university, or work might be a useful screen for cognitive impairment in Wilson's disease. Commonly used bedside tests such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) are less sensitive for mild cognitive impairment, and more detailed assessments with the Addenbrooke's Cognitive Examination or formal neuropsychometry might be required.<sup>38</sup>

Behavioural or personality changes (ie, incongruous behaviour, irritability, aggression, and disinhibition),

mood disorders (eg, hypomania or depression), and anxiety are common.<sup>39,40</sup> Psychosis can also occur, typically with paranoid delusions.<sup>41</sup> Psychiatric features often go unnoticed, particularly in the paediatric population in which changes in behaviour or mood could be attributed to adolescence.<sup>42</sup> In a large retrospective study of patients with Wilson's disease from the UK, 51% had psychiatric symptoms at the time of diagnosis and 20% had previously seen a psychiatrist.<sup>40</sup> Although the yield from screening patients with isolated psychiatric symptoms is low,<sup>43</sup> psychiatrists should be aware of hepatic and neurological features and urgently arrange initial investigations and onward referral if Wilson's disease is suspected.

We suggest that all patients between the age of 5 years and 50 years who develop a progressive postural tremor, dystonia, or parkinsonism, except individuals with isolated cervical dystonia or blepharospasm, should have routine investigations for Wilson's disease (recommendation 1.5; table 1). All patients who develop a mixed movement disorder with any red flags (ie, subacute onset or progression, early bulbar involvement, executive dysfunction, behavioural or personality changes, or suspected liver disease) should have routine investigations and a wider screen for Wilson's disease, in addition to neuroimaging (recommendation 1.6; table 1).

#### Haemolysis

A Coombs-negative haemolytic anaemia occurs in 4–10% of cases and is more common in presentations during childhood or adolescence.<sup>23,44,45</sup> When associated with unexplained liver disease or movement disorders, it is highly suggestive of Wilson's disease. The clinical course could be with an acute haemolytic syndrome or insidious with previous episodes of unexplained jaundice. In a retrospective analysis of 321 patients, haemolysis was the initial presentation in 22 cases and the diagnosis of Wilson's disease was frequently delayed with subsequent progressive liver injury or neurological deterioration.<sup>46</sup> All patients with an unexplained Coombs-negative haemolytic anaemia should have routine investigations and a wider screen for Wilson's disease (recommendation 1.7; table 1).

### Interpreting initial investigations

#### Liver function tests

Abnormal liver biochemistry is a well recognised but non-specific feature of Wilson's disease. Crucially, normal liver function tests do not exclude the diagnosis of Wilson's disease: elevated aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), typically ranging between 50–200 U/L,<sup>23</sup> are only found in 60% of patients with hepatic presentations and 30% of patients with neurological presentations.<sup>22</sup> Hyperbilirubinaemia, which is present in 20–50% of cases, can reflect liver injury, Coombs-negative haemolysis, or a combination of these in patients with

Wilson's disease.<sup>22,23</sup> Measuring the relative proportions of conjugated and unconjugated bilirubin is helpful when haemolysis is suspected.

#### Full blood count and clotting profile

Haematological abnormalities are common in Wilson's disease, occurring in a third of patients at diagnosis.<sup>21</sup> Thrombocytopenia and, less commonly, leukopenia, occur in the setting of portal hypertension. Elevated prothrombin time and international normalised ratio can also occur in parallel with hepatic dysfunction.<sup>46</sup> Patients with haemolysis will typically have a macrocytic anaemia associated with a reticulocytosis.

#### Serum caeruloplasmin

A very low serum caeruloplasmin (<0.10 g/L) is characteristic of Wilson's disease.<sup>47</sup> However, patients often have intermediate concentrations (0.10–0.20 g/L) and up to 15% of individuals with neurological presentations and 40% of those with hepatic presentations have concentrations in the normal range (>0.20 g/L).<sup>21,48</sup> Systemic inflammation and the effect of oestrogens during pregnancy or oral contraceptive pill use can increase caeruloplasmin concentrations into the normal range in patients with Wilson's disease.<sup>49</sup> Conversely, reduced levels between 0.10–0.20 g/L can be found in end-stage liver disease of any cause, in addition to copper deficiency due to gastrointestinal malabsorption or dietary zinc supplementation. Up to 30% of heterozygous *ATP7B* carriers have a serum caeruloplasmin of 0.15–0.19 g/L and variants in the caeruloplasmin gene can also cause reduced or undetectable concentrations.<sup>50</sup> Patients with bi-allelic caeruloplasmin gene mutations develop acaeruloplasminaemia, which is a very rare neurodegenerative disease associated with abnormal iron metabolism, anaemia, and diabetes.<sup>51</sup>

In light of all of these limitations, the positive predictive value of serum caeruloplasmin below 0.20 g/L for the diagnosis of Wilson's disease among adults being investigated for liver disease is only 6%.<sup>52</sup> A wider screen for Wilson's disease is usually required to confirm the diagnosis in patients with serum caeruloplasmin of less than 0.10 g/L (recommendation 2.1; table 1) and is indicated in patients with serum caeruloplasmin of 0.10–0.20 g/L (recommendation 2.2; table 1). Serum caeruloplasmin of more than 0.20 g/L does not exclude a diagnosis of Wilson's disease but reduces the likelihood of it (recommendation 2.3; table 1).

#### 24-h urinary copper output

Urinary copper output varies throughout the day and 24-h urine collections are required. Although laboratories often insist on using acid-washed containers, this requirement has in the last 2 years been shown to be unnecessary.<sup>53</sup> Patients should be offered written instructions for 24-h urine collections (see appendix p 1) and provided with non-acid-washed containers (recommendation 2.4, table 1).

With a cut-off of 0.64  $\mu\text{mol}/24\text{ h}$  (40  $\mu\text{g}/24\text{ h}$ ), urinary copper output has sensitivity 79% and specificity 88% for diagnosing Wilson's disease in children.<sup>47</sup> Data confirming an appropriate cut-off in adults are scarce,<sup>47</sup> but mean copper output was 0.34  $\mu\text{mol}/24\text{ h}$  (21  $\mu\text{g}/24\text{ h}$ ) in a study of 111 healthy adults from the UK,<sup>54</sup> and most clinical biochemists would consider a copper output of more than 0.64  $\mu\text{mol}/24\text{ h}$  (40  $\mu\text{g}/24\text{ h}$ ) to be abnormal in an adult as well. Cholestasis prevents the biliary excretion of copper and can lead to systemic copper overload with markedly elevated urinary copper output, particularly in children.<sup>55</sup> Other causes of increased urinary copper output include autoimmune hepatitis and non-alcoholic fatty liver disease.<sup>56</sup> We recommend that a copper output of more than 0.64  $\mu\text{mol}/24\text{ h}$  (40  $\mu\text{g}/24\text{ h}$ ) is suggestive of Wilson's disease but further investigations are required to make a diagnosis (recommendation 2.5; table 1).

#### Slit lamp examination

Copper deposits within Descemet's membrane, known as Kayser–Fleischer rings, are seen on slit-lamp examination in 90% of neurological presentations and 47% of hepatic presentations and are highly suggestive of Wilson's disease (recommendation 2.6; table 1).<sup>48,57</sup> They can also occur with systemic copper overload due to cholestasis and, very rarely, alcohol-related hepatitis and multiple myeloma.<sup>58,59</sup> They are often visible with the naked eye as a yellowish-green or golden-brown discoloration at the periphery of each cornea, which on close inspection is distinct from the underlying iris. A tentative diagnosis of Wilson's disease based on the presence of Kayser–Fleischer rings can therefore take place at the bedside before being confirmed with slit lamp examination by an experienced ophthalmologist.

#### Have I made the diagnosis yet?

The diagnosis of Wilson's disease is straightforward when there is a low serum caeruloplasmin (<0.20 g/L), high urinary copper output (>0.64  $\mu\text{mol}/24\text{ h}$  or 40  $\mu\text{g}/24\text{ h}$ ), and Kayser–Fleischer rings.<sup>60</sup> A typical neurological presentation with either a very low serum caeruloplasmin (<0.1 g/L) or Kayser–Fleischer rings is also considered diagnostic of Wilson's disease. Otherwise, several additional investigations might need to be considered. The Leipzig scoring system could be helpful here (appendix p 1). However, we recommend that this scoring system is used in conjunction with discussion with a clinician experienced in managing Wilson's disease given some additional investigations are invasive or time-consuming, and could delay the initiation of treatment unnecessarily.<sup>61</sup> Consolidating expertise in hepatology and movement disorders into paediatric and adult centres for Wilson's disease can help with diagnosis and management, and provides patients

with opportunities to participate in clinical research and trials. This approach has been successfully implemented in England (appendix p 2).

#### How urgent is the situation?

A suspected diagnosis of Wilson's disease should be taken seriously. Complications can rapidly develop, even after many years of subclinical disease. These complications can be fatal, particularly in the context of acute liver failure, or lead to irreversible neurological disability. Initial investigations should be performed as soon as possible given the risk of hepatic and neurological deterioration (recommendation 2.7; table 1) and patients suspected to have Wilson's disease should be urgently discussed with a specialist centre (recommendation 2.8; table 1). All newly diagnosed cases must be discussed before or soon after treatment initiation. Patients should also be encouraged to contact a patient advocacy service such as the Wilson's Disease Support Group UK, which offers support for people living with Wilson's disease and their families.

For more on the Wilson's Disease Support Group see [www.wilsonsdisease.org.uk](http://www.wilsonsdisease.org.uk)

#### Additional investigations

##### Serum copper

Additional investigations might be indicated in a patient with suspected Wilson's disease. Serum copper concentration reflects copper incorporated into caeruloplasmin and non-caeruloplasmin-bound copper. Patients with a low serum caeruloplasmin usually have a low serum copper, irrespective of the underlying cause, and so serum copper should not routinely be used alone to confirm or exclude a diagnosis of Wilson's disease (recommendation 3.1; table 1).<sup>62</sup> In patients with Wilson's disease, normal copper with low serum caeruloplasmin concentration indicates a very high non-caeruloplasmin-bound concentration, which is often associated with severe acute liver injury and haemolysis.<sup>46,63</sup> The non-caeruloplasmin-bound copper can be calculated in  $\mu\text{mol}/\text{L}$  by subtracting the serum caeruloplasmin in g/L multiplied by 47 from the serum copper in  $\mu\text{mol}/\text{L}$ .<sup>64</sup> A factor of 3.15 is used with serum copper in  $\mu\text{g}/\text{dL}$  and caeruloplasmin in mg/dL.<sup>10</sup> The non-caeruloplasmin-bound copper is useful for monitoring treatment response but variation in the sensitivity and specificity of caeruloplasmin assays between laboratories makes deriving a universal cut-off value for diagnostic purposes problematic.<sup>64</sup> Clinicians should not delay initiation of treatment while serum copper test results are pending (recommendation 3.2; table 1).

##### Genetic testing

More than 700 pathogenic mutations in *ATP7B* have been described. In a genetic study<sup>65</sup> of 181 patients from the UK, two mutations were identified in 98% of participants when using a combination of Sanger sequencing (including coding regions, splice sites, and promoter region) and multiplex ligation-dependent

probe amplification (for identifying deletions and duplications). However, data about the pathogenicity of some variants is based on individual case reports and several common variants appear to exhibit reduced clinical penetrance.<sup>66</sup> Genetic testing is also expensive and time-consuming. Despite these limitations, *ATP7B* sequencing has an important role in confirming the clinical diagnosis and is helpful when initial investigations are inconclusive and for family screening.<sup>67</sup> We advocate that genetic testing is required in all patients suspected to have Wilson's disease on clinical and biochemical grounds but should not delay the initiation of treatment (recommendation 3.3; table 1). Clinicians should be aware that a genetic diagnosis of Wilson's disease should always be corroborated with clinical and biochemical findings, and the absence of two pathogenic mutations does not exclude a diagnosis of Wilson's disease.

#### *Liver imaging and transient elastography*

Ultrasound has an important role in staging liver disease severity and all patients with suspected Wilson's disease should have a liver ultrasound scan irrespective of their clinical presentation (recommendation 3.4, table 1). Hepatic steatosis is the most common finding seen in 35–88% of patients.<sup>68,69</sup> Cirrhosis could be suggested by an irregular liver edge, reversed portal vein flow, increased spleen size, or the presence of ascites. CT or MRI can also show intra-abdominal collaterals or varices suggestive of elevated portal pressure. Even patients with exclusively neurological features have a high rate of liver abnormalities on imaging.<sup>22</sup> Multiple hyperechoic and hypoechoic nodular lesions, a perihepatic fat layer, and the absence of caudate lobe hypertrophy in a cirrhotic liver have been suggested to be specific for Wilson's disease. However, these findings have only been shown in small series and should not be considered diagnostic.<sup>68,70</sup>

Liver stiffness measurement by transient elastography is an additional tool for non-invasive fibrosis staging and should be performed in all adults without overt cirrhosis at the point of Wilson's disease diagnosis (recommendation 3.5; table 1). A liver stiffness measurement cut-off greater than or equal to 9.9 kPa has good accuracy in identifying cirrhosis in newly diagnosed adults.<sup>71</sup> Liver stiffness measurement is stable over time in most chronically treated patients and routine monitoring could be unnecessary unless there are concerns about treatment non-adherence or disease progression.<sup>71</sup> There is a shortage of studies evaluating the performance of liver stiffness measurement in children with Wilson's disease.

#### *Neuroimaging*

Hyperintense signal abnormalities in the basal ganglia, thalamus, and brainstem are seen on T2-weighted or fluid attenuated inversion recovery sequences of 90% of

patients with neurological presentations but can also be found in patients without neurological or psychiatric symptoms (figure 2).<sup>72–74</sup> When seen in the posterior midbrain, pons, or simultaneously involving the basal ganglia and brainstem, these findings appear to be highly specific for Wilson's disease.<sup>75</sup> Wilson's disease should therefore be considered in any patient with an unexplained movement disorder and signal abnormalities in basal ganglia, thalamus, or brainstem (recommendation 3.6; table 1). The pathognomonic so-called face of the giant panda sign is present in only 12% of cases.<sup>74</sup> Wilson's disease can rarely cause confluent white matter abnormalities.<sup>76,77</sup> Brain atrophy and susceptibility-weighted imaging abnormalities are also common at diagnosis and correlate with neurological severity at diagnosis.<sup>78</sup> T1-weighted hyperintensities in the basal ganglia, which are likely to represent manganese deposition and can occur with cirrhosis of any cause, can also be seen.<sup>79–81</sup> We suggest that an MRI brain scan is indicated in any patient with suspected Wilson's disease who has neurological or psychiatric manifestations (recommendation 3.7; table 1), and all patients with a confirmed diagnosis of Wilson's disease should have an MRI brain scan, irrespective of their initial presentation (recommendation 3.8; table 1).

#### *Liver biopsy*

Steatosis might be the only histopathological feature of liver disease in the early stages of Wilson's disease, although this is often seen alongside portal inflammation and fibrosis.<sup>24</sup> Copper and copper-associated proteins could be identified by histochemical stains (eg, rhodamine or orcein). However, staining for copper and copper-associated proteins can also be seen in heterozygous *ATP7B* carriers and in a range of cholestatic disease, and is absent in some patients with Wilson's disease. Histological appearances cannot rule out Wilson's disease and measurement of hepatic parenchymal copper concentration is required if Wilson's disease is being considered. The normal copper content of the liver is less than 50 µg/g of dry weight and at least 250 µg/g has traditionally been regarded as diagnostic of Wilson's disease.<sup>24</sup> However, a large prospective study has shown that a cut-off value of 209 µg/g dry weight has 99% sensitivity and 96% specificity for diagnosing Wilson's disease among patients with non-cholestatic liver diseases.<sup>82</sup>

We suggest that hepatic parenchymal copper quantification could help with the diagnosis of Wilson's disease when other non-invasive tests have proved inconclusive (recommendation 3.9; table 1). In the absence of cholestatic liver disease, a cut-off value of 209 µg/g dry weight should be used (recommendation 3.10; table 1). A percutaneous approach is preferable unless there is a concern for bleeding risk or ascites when a transjugular biopsy can be considered. A practical guide to the processing of



liver tissue for parenchymal copper quantification, including common pitfalls, is presented in the appendix (p 2). A liver biopsy might also be needed in patients with a confirmed diagnosis of Wilson's disease when there is clinical uncertainty about the presence or absence of cirrhosis (recommendation 3.11; table 1). It is not indicated in patients with a confirmed diagnosis of Wilson's disease who have no evidence of liver involvement (recommendation 3.12; table 1).

#### Copper-65 absorption test

This test involves administering an oral solution of a non-radioactive isotope of copper ( $^{65}\text{Cu}$ ) and measuring the  $^{65}\text{Cu}$  to  $^{65}\text{Cu}$  ratio in serum samples over 72 h. Patients with Wilson's disease have a characteristic pronounced early peak before a gradual decline as they cannot incorporate  $^{65}\text{Cu}$  into caeruloplasmin whereas healthy controls and heterozygote carriers have a gradual increase in the ratio as  $^{65}\text{Cu}$  is incorporated into caeruloplasmin. This test has been validated in a cohort of 13 patients with Wilson's disease, 12 heterozygote carriers, and ten healthy controls from the UK.<sup>83</sup> Some experts on the panel have found this test invaluable in difficult cases. We suggest that the copper-65 test can be performed in specialist centres when other tests are inconclusive and clinical suspicion remains (recommendation 3.13; table 1). A radioactive copper incorporation test is available in some other countries (eg, Poland).<sup>84</sup>

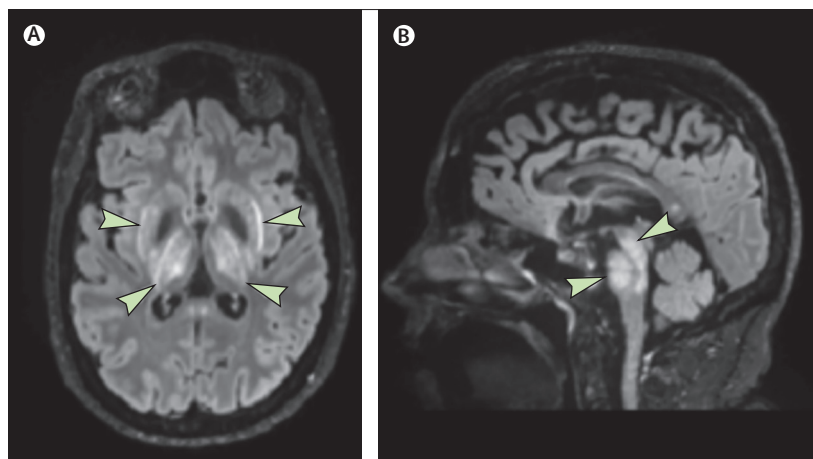
#### Penicillamine challenge test

Historically, urinary copper excretion was measured following the administration of penicillamine as part of the diagnostic work-up of Wilson's disease. However, results have proved unreliable and this test is no longer recommended for symptomatic or asymptomatic patients with suspected Wilson's disease.

#### Initial management

##### Acute liver failure

Acute liver failure is a medical emergency that requires early recognition, rapid diagnostic work-up, and prompt supportive management. All children with paediatric acute liver failure or decompensated liver disease should be urgently referred to a paediatric liver transplant centre (recommendation 4.1, table 1; appendix p 3). Adults with acute liver failure should be urgently referred to an adult liver transplant centre (recommendation 4.2, table 2; appendix p 3). All patients require urgent imaging to examine liver texture and vasculature. Kayser–Fleischer rings are present in half of patients with Wilson's disease who are in acute liver failure, and urinary copper is usually markedly elevated. Slit-lamp examination and 24-h urine collection should therefore be attempted in patients with acute liver failure in which the underlying cause is not immediately apparent, even in the emergency setting. Transjugular



**Figure 2: Neuroimaging abnormalities in Wilson's disease**

Neuroimaging abnormalities in Wilson's disease. Axial (A) and sagittal (B) views of a fluid attenuated inversion recovery sequence show hyperintense signal abnormality in the basal ganglia, thalamus, and brainstem (arrowheads). The images are included with patient consent, and have been provided by Dr Samuel Shribman.

liver biopsy with copper staining can be useful for providing urgent histological support for a diagnosis of Wilson's disease with later validation through quantification of parenchymal copper content.

Liver transplantation is indicated in children who have decompensated liver disease with encephalopathy (recommendation 4.3; table 1) and should be considered in all adults with acute liver failure (recommendation 4.4; table 1). Decisions to transplant patients who are not encephalopathic can be difficult. The new Wilson index is accurate in predicting mortality with listing for liver transplantation recommended for patients with a score 11 or greater and should be used for prognosis and to facilitate decision making for liver transplantation in children (recommendation 4.5; table 1; appendix p 3).<sup>26,85</sup> Plasmapheresis, renal replacement therapy, exchange transfusion, and artificial liver support systems have been used as bridging therapy for patients with Wilson's disease awaiting a liver transplant with mixed results.<sup>86–89</sup> Medical treatment with chelation therapy (with or without zinc salts) should be used in patients with acute hepatic Wilson's disease without encephalopathy in an attempt to avoid liver transplantation.<sup>26</sup> Issues related to transplantation allocation, post-transplantation care, and the potential role for transplantation with neurological indications are beyond the scope of this Review.

#### Chelation therapy

Chelating agents mobilise intracellular copper into the circulation and enhance urinary excretion of copper. The primary treatment goals are to induce adequate urinary copper excretion, arrest the disease process, and reduce symptom burden while minimising adverse effects. After a period of sustained clinical and biochemical response, typically at least 2 years, the aim is to prevent disease

|               | Children  | Adults without neurological or psychiatric symptoms   | Adults with neurological or psychiatric symptoms  | Maintenance dose (typically after 2 years)  | Adverse effects   |
|---------------|---|---|---|---|---|
| Penicillamine | 125–250 mg per day slowly increasing by 125–250 mg per week to 20 mg/kg per day in two divided doses (maximum 1500 mg/day)  | 1000–1500 mg per day in two divided doses   | 125–250 mg per day, slowly increasing by 125–250 mg per week, to 1000–1500 mg per day in two divided doses  | 10–20 mg/kg per day in two divided doses  | Early reactions: hypersensitivity reactions (fever and rash), proteinuria, bone marrow suppression (thrombocytopenia and neutropenia), altered sense of taste or smell, and paradoxical neurological worsening. Late reactions: lupus-like syndrome, Goodpastures syndrome, elastosis perforans serpiginosa, cutis laxa, and poor wound healing |
| Trientine     | 150–200 mg per day, slowly increasing by 150–200 mg per week to 400–1000 mg per day for trientine dihydrochloride (Cufence) or 225–600 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses | 800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses | 150–200 mg per day, slowly increasing by 150–200 mg per week to 800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses | 800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses | Urticaria or other rashes, arthralgia, myalgia, proteinuria, haematuria, sideroblastic anaemia, and paradoxical neurological worsening  |
| Zinc salts    | 25 mg daily if patient <6 years; 25 mg three times daily if patients aged 6–16 years or <50 kg; 50 mg three times daily if patient >16 years or >50 kg  | 50 mg three times daily if patient >50 kg   | 50 mg three times daily if patient >50 kg   | 25–50 mg three times a day  | Nausea, abdominal pain, gastritis, and paradoxical neurological worsening   |

Dosing for penicillamine and zinc salts are based on experience of the authors, and dosing for trientine dihydrochloride and trientine tetrahydrochloride on the basis of the summary of product characteristics by the manufacturer. The recommended doses of trientine dihydrochloride and tetrahydrochloride are expressed as mg of trientine base as opposed to trientine salt. Chelating agents and zinc salts should be taken on an empty stomach.

**Table 2: Dosing and adverse effects for penicillamine, trientine, and zinc salts**

progression with the lowest effective dose, ensuring adherence is always maintained. Chelation therapy is not required in patients who have been successfully treated with liver transplantation.

The most commonly used chelating agents are penicillamine and trientine. Both agents must be taken on an empty stomach. There are no randomised controlled trials comparing their efficacy, and data from retrospective studies are conflicting. Clinicians in the UK tend to have more experience with penicillamine, which is substantially cheaper than trientine but adverse effects leading to drug discontinuation are more frequent.<sup>90,91</sup> Because of the increase in cost of trientine, NHS England published a clinical commissioning policy limiting its use in 2018. As a result, penicillamine monotherapy is considered first-line treatment for children and adults in the UK (recommendation 4.6; table 1). Trientine can be used in children and adults who are intolerant to penicillamine or at increased risk of adverse effects (recommendation 4.7; table 1). Specific examples of penicillamine intolerance are provided in the appendix (p 4). Patients with a history of autoimmune diseases, severe thrombocytopenia, or renal disease and allergy to penicillin are thought to have an increased risk of adverse effects with penicillamine.<sup>92</sup>

The dose of trientine in previous guidelines<sup>7–10</sup> refers to the trientine dihydrochloride salt. However, an alternative formulation, trientine tetrahydrochloride, has become available and the European Medicines Agency approval now requires trientine dihydrochloride and trientine tetrahydrochloride to be labelled with respect to the

trientine base. Trientine dihydrochloride labelled according to the salt content is available in the UK and other countries, and so clinicians should always check if doses refer to the base or salt when prescribing trientine. In addition, the bioavailability of the trientine base differs between trientine dihydrochloride and trientine tetrahydrochloride, and so doses are not equivalent even when referring to the trientine base.<sup>93</sup> The bioavailability of both drugs could also be diminished by trientine–diet interactions.

There are no universally accepted dosing schedules for penicillamine or trientine and most adverse effects are dose-dependent (table 2). The general rule is to start low and go slow, aiming to reach the initial target dose in 4–6 weeks. We recommend penicillamine dose increments of 125–250 mg per week in children (recommendation 4.8; table 1) and in adults presenting with neurological or psychiatric symptoms (recommendation 4.9; table 1). Penicillamine can be introduced more quickly in adults presenting with decompensated liver disease in the absence of neurological symptoms or neuroimaging abnormalities (recommendation 4.10; table 1). Patients do not necessarily need to be admitted to hospital to initiate treatment, but they do need close monitoring. A full blood count, liver function tests, renal profile, and urine dipstick should be done to monitor for adverse effects before starting penicillamine, after 1 week of treatment, and then every 2 weeks for 3 months (recommendation 4.11; table 1). Patients should be offered clear information on the risks, monitoring, and outcomes associated with these treatments at the outset

and given a point of contact from a specialist centre if starting treatment in the community. We recommend reviewing the checklist in the appendix (p 4) for all patients starting chelation therapy.

Some clinicians offer pyridoxine (vitamin B6) supplements to patients being treated with penicillamine on the basis that high doses have been shown to disrupt pyridoxine metabolism. The evidence to support this is scarce.<sup>94</sup> Prophylactic supplementation with 50 mg once a day could be warranted in patients requiring doses higher than 40 mg/kg and those at increased risk of vitamin B6 deficiency through pregnancy, breastfeeding, or malabsorption.

#### Zinc salts

Zinc salts inhibit the absorption of dietary copper by increasing metallothionein expression in enterocytes. The role of zinc salts in the treatment of Wilson's disease is controversial given that monotherapy prevents progression of liver disease in some cohorts but not others.<sup>95-97</sup> They are considered a third-line treatment for adults in the UK and should only be initiated by specialist centres (recommendation 4.12; table 1). They are not recommended as monotherapy in patients with cirrhosis unless other treatments are contraindicated. We cannot make a strong recommendation for the use of zinc salts in children because of inadequate data (recommendation 4.13; table 1). We recognise that they are commonly used in children and adults in other countries (eg, Poland) where chelating agents are unavailable or not deemed to be cost-effective, and could have a role as first-line treatment in carefully selected paediatric cases.

#### Dietary copper restriction

A low-copper diet has long been considered an important aspect of the management of Wilson's disease. However, there are no randomised controlled trials supporting this strategy. Most clinicians in Europe advise dietary copper restriction for at least the first year of treatment or until liver function tests normalise.<sup>98</sup> The literature mentions avoiding chocolate, nuts, liver (and other offal), shellfish, and mushrooms.<sup>7,10</sup> We suggest that dietary copper intake should be restricted in the first year of treatment (recommendation 4.14; table 1). Decisions to continue dietary copper intake after 1 year should consider response to treatment, adherence, and impact on quality of life. The Wilson's Disease Support Group UK has published a table outlining the approximate copper content in specific foods to aid patients and their families. Referral to a dietitian can be helpful for patients requiring additional support.

#### Paradoxical neurological worsening

Between 11% and 30% of patients with neurological or psychiatric symptoms at presentation develop paradoxical neurological worsening, which can be irreversible, in the first 6 months after initiation of treatment.<sup>99-101</sup> The

complication can occur with penicillamine, trientine, and zinc salts, and data on the risk of worsening with each treatment are conflicting.<sup>90,102</sup> The pathophysiological basis for this phenomenon is unclear but risk factors can include severe neurological involvement at baseline, brainstem and thalamic lesions on MRI, and concurrent antipsychotic use.<sup>99</sup> It can also be difficult to differentiate between underlying disease progression (ie, undertreatment) or paradoxical worsening when patients deteriorate soon after treatment initiation.

There is a consensus among experts that rapidly escalating doses could provoke or exacerbate worsening, but there is insufficient data to guide how clinicians should respond when patients deteriorate. Clinicians might need to consider the disease course before treatment initiation, the current dose relative to the target dose, the severity of the deterioration, and the risk of hepatic decompensation when deciding whether to continue, decrease, or increase the dose, switch treatments, or consider other options with anecdotal evidence, such as a course of intramuscular dimercaprol.<sup>103</sup> It is unclear whether a liver transplant should be done to treat patients with paradoxical neurological worsening or severe neurological worsening resistant to active chelation therapy.<sup>104</sup> Patients with neurological symptoms should have regular follow up with a movement disorders specialist for a minimum of 12 months after treatment initiation (recommendation 4.15; table 1).

#### Response to treatment

Chelation therapy is usually effective for managing liver disease but neurological outcomes are less predictable.<sup>105</sup> The delay between treatment initiation and clinical response is variable but liver function tests and neurological symptoms usually begin to improve within 6 months. It can take several years before neurological recovery reaches a plateau.<sup>106</sup>

The 24-h urinary copper output and non-caeruloplasmin-bound (free) copper can be used to monitor the biochemical response to treatment. Chelation therapy induces a marked increase in urinary copper excretion (cupriuresis) in the first few months, which typically peaks at around 6 months with penicillamine and 18 months with trientine.<sup>107</sup> Urinary copper output can either be measured while continuing medication (on treatment) or after 48 h of treatment cessation (off treatment).<sup>108</sup> We suggest measuring the 24-h urinary copper output while continuing medication (on treatment) within the first 2 months to confirm there is an adequate cupriuresis (recommendation 4.16; table 1). On treatment copper output is usually more than 8  $\mu\text{mol}$  (500  $\mu\text{g}$ ) per 24 h after reaching the target dose of penicillamine. Off treatment copper output, which is thought to indicate the residual copper load, decreases over the first and second year of treatment for patients on penicillamine but takes longer for patients

For the Wilson's Disease Support Group UK food information see <https://www.wilsonsdisease.org.uk/Site/Pages/diet>

on trientine.<sup>107</sup> It is not usually helpful to measure this in the first 6 months of treatment. The non-caeruloplasmin-bound (free) copper should gradually decrease with treatment.

### Long-term management

#### Follow up

Patients established on treatment should be followed up every 6–12 months. Patients with decompensated liver disease, substantial neurological disability or non-adherence could require more frequent monitoring. Follow up should include clinical assessment, measurement of body weight, urine dipstick, and blood tests, including a full blood count, liver function tests, coagulation profile, renal function, bone profile, serum caeruloplasmin, and serum copper. It might be helpful to video-record the neurological examination and use the Unified Wilson's Disease Rating Scale to monitor the neurological response to treatment. Adherence and any wider concerns about medications should be addressed given non-adherence leads to progression of liver disease and neurological symptoms, and is the second most common cause of death in patients with Wilson's disease after diagnostic failure.<sup>109–114</sup> 24-h urine copper output should be measured on at least an annual basis to confirm compliance and adjust dose if required. The presence of Kayser–Fleischer rings should be re-examined at the bedside to document if and when they resolve and vitamin D supplements should be encouraged given that metabolic bone disease is common in Wilson's disease.

#### Copper indices

Clinicians vary in whether they recommend on treatment or off treatment collections during maintenance therapy. Results from on treatment collections can be misleading if patients are non-adherent to treatment around the time of the collection. An off treatment collection should be done when the urinary copper output is unexpectedly high or low in an on treatment collection and might therefore be preferable in the first instance. There is insufficient evidence to guide treatment targets for either approach. A safe copper output for one patient could be harmful for another, and the overall trend could be more important than the exact value. Nonetheless, values above the targets in the following recommendations could indicate undertreatment or non-adherence: 24-h urinary copper output while continuing medications (on treatment) should be 3–8  $\mu\text{mol}/24\text{ h}$  (200–500  $\mu\text{g}/24\text{ h}$ ) with chelating agents and 0.5–1.2  $\mu\text{mol}/24\text{ h}$  (30–75  $\mu\text{g}/24\text{ h}$ ) with zinc salts (recommendation 5.1; table 1). 24-h urinary copper output after 48 h of treatment cessation (off treatment) should be 0.2–0.6  $\mu\text{mol}/24\text{ h}$  (12–40  $\mu\text{g}/24\text{ h}$ ) for patients treated with chelating agents (recommendation 5.2; table 1). Non-caeruloplasmin-bound copper should be less than 2.4  $\mu\text{mol}/\text{L}$  (15  $\mu\text{g}/\text{dL}$ ; recommendation 5.3; table 1).

Some patients require high doses of chelating agents and are then at risk of dose-dependent long-term adverse effects. For example, patients taking high doses of penicillamine are at risk of elastosis perforans serpiginosa and cutis laxa. Iatrogenic copper deficiency manifesting with pancytopenia and myelopathy has also been reported.<sup>115</sup> An off treatment urinary copper output of less than 0.2  $\mu\text{mol}/24\text{ h}$  (12  $\mu\text{g}/24\text{ h}$ ) could indicate overtreatment. Patients should be carefully monitored if doses are reduced.

#### Multidisciplinary team

Patients with Wilson's disease, including those treated with a liver transplant, need to be followed up in a dedicated multidisciplinary team clinic typically consisting of hepatologists, neurologists, and experts in inherited metabolic disease. Some patients will have particularly complex needs, which require the input of additional services including psychiatry, clinical psychology, speech and language therapy, physiotherapy, occupational therapy, dietetic, and vocational rehabilitation services. Clear care pathways should be established locally to ensure reliable and timely access to professionals in these associated specialties.

#### Neurological and psychiatric symptoms

Some medicines commonly used to treat neurological and psychiatric symptoms, such as benzodiazepines, tricyclic antidepressants, and valproate, are metabolised by the liver and should be used with caution in patients with cirrhosis; other medications (eg, antipsychotics) can exacerbate movement disorders. Clinicians should also be aware that some neurological symptoms, particularly tremor,<sup>111</sup> are more likely to improve with chelation therapy than others. Deep brain stimulation surgery could be appropriate for a minority of carefully selected patients with persistent, disabling tremor or dystonia despite symptomatic treatments and several years of intensive chelation therapy.<sup>116–118</sup> Patients with neurological symptoms that impede safe driving should be advised to contact their licensing authority.

#### Hepatocellular carcinoma screening

Hepatocellular carcinoma is a major complication of cirrhosis; however, the specific risk of hepatocellular carcinoma in Wilson's disease is widely regarded as being low compared with other causes of chronic liver disease.<sup>25,105,119</sup> Nonetheless, hepatocellular carcinoma is a well-recognised complication of Wilson's disease, occurring nearly exclusively in patients with cirrhosis,<sup>120</sup> and UK electronic health record data have identified hepatocellular carcinoma as the underlying cause of death in three (6%) of 52 patients with Wilson's disease between 2008 and 2018.<sup>121</sup> We therefore suggest hepatocellular carcinoma screening is appropriate in patients with Wilson's disease and established cirrhosis (recommendation 5.4; table 1), particularly in the

presence of additional co-factors such as alcohol or features of metabolic syndrome. Screening should be performed every 6 months using ultrasound in line with international guidelines for hepatocellular carcinoma screening in cirrhosis.<sup>122</sup>

#### Family planning and pregnancy

Preparation for pregnancy in patients with Wilson's disease should include careful optimisation of copper status. Although historically there have been some concerns about teratogenicity of chelation therapy, particularly with penicillamine, teratogenicity has not been clearly shown in published series.<sup>123–126</sup> Conversely, drug discontinuation during pregnancy has been associated with acute liver failure.<sup>125,127</sup> The benefits of continuing chelation therapy throughout pregnancy outweigh the theoretical risks and we advocate that chelation therapy should be continued throughout pregnancy (recommendation 5.5; table 1). There is no evidence that breast feeding while taking chelation therapy is harmful. Women on chelation therapy should not be advised against breastfeeding (recommendation 5.6; table 1).<sup>128</sup>

#### Family screening

Each sibling of an affected patient has a 25% chance of having Wilson's disease and should be offered screening for Wilson's disease. Pseudo-dominant inheritance with diagnoses across multiple generations has been described, and screening is therefore usually extended to other first-degree relatives, including parents and offspring. Up to 69% of patients diagnosed through family screening have clinical features of liver disease or neurological disease.<sup>14</sup> Some patients require urgent investigations and initiation of treatment. We therefore recommend that clinical assessment, routine investigations, and genetic screening should be offered to all first-degree relatives of patients diagnosed with Wilson's disease (recommendation 6.1; table 1). Slit lamp examination and 24-h urine collection for copper should also be considered, especially in siblings of index cases. Treatment of asymptomatic patients should only be initiated by specialist centres (recommendation 6.2; table 1).

Genetic screening for Wilson's disease should be arranged through a clinical genetics service and follow standard practice for autosomal recessive conditions. Genetic testing can be helpful to confirm that both parents are heterozygous carriers and hence that variants identified in the index case are in trans (on separate chromosomes), in addition to diagnosing Wilson's disease in siblings and other first-degree relatives. Parents should then be asked to contact their own siblings to make them aware that they have a chance of being a Wilson's disease carrier and that they should be referred for family screening. Risks to relatives outside of the nuclear family are likely to be low unless there is a history of consanguinity. Partners of index patients or

heterozygous carriers might wish to undergo genetic screening when planning a family. These individuals should also be referred to a clinical genetics service. It might be appropriate to discuss reproductive medicine options for couples who are carriers of *ATP7B* variants.

#### Future directions

Over the past decade, advances in the diagnosis and management of Wilson's disease could influence mainstream practice in the near future. Direct measurement of *ATP7B* peptides using dried blood spot samples has been shown to differentiate patients with Wilson's disease from healthy controls with high sensitivity and specificity, and could have a role in initial screening or confirmatory testing for Wilson's disease.<sup>129</sup> Anterior segment ocular coherence tomography appears to be more sensitive than slit-lamp examination for the detection of Kayser–Fleischer rings but is not yet widely available.<sup>130</sup> Wet (fluid) and imaging biomarkers for neurological involvement are in development and could be used to guide treatment decisions or as endpoints in clinical trials.<sup>131</sup> Finally, drug therapies are being tested: a phase 3 trial comparing bis-choline tetrathiomolybdate to standard of care has is ongoing (NCT03403205), as is an open-label phase 1/2 trial for adeno-associated viral vector-based gene therapy (NCT04537377). We anticipate that further collaboration between specialist centres, both nationally and internationally, will be needed to maximise opportunities for translational research and participation in clinical trials going forward.

#### Conclusions

Wilson's disease is a rare and complex disorder that requires early recognition and treatment to prevent critical hepatic and neurological complications. Many patients with this condition will first present to primary and secondary care, and it is crucial that general physicians are familiar with the spectrum of clinical manifestations, indications for testing, and diagnostic tools available. This multidisciplinary guidance, supported by major hepatology and neurology societies, provides a clear, practical, and accessible framework for the investigation of individuals with suspected Wilson's disease. It also emphasises the need for early consultation with specialist centres to establish the diagnosis, initiate treatment, and establish long-term pathways for follow up. Our advice reflects data on imaging abnormalities in the liver and brain, cut-offs for hepatic copper quantification, *ATP7B* variants, paradoxical neurological worsening, and the relative efficacy of common therapies in Wilson's disease.<sup>66,71,72,82,91,99</sup> The guidance also considers broader changes in clinical practice associated with increasing access to transient elastography, neuroimaging, and genetic testing, and decreasing reliance on liver biopsy and penicillamine challenge tests. Through promoting greater awareness of the challenges and pitfalls of Wilson's disease management, we hope to

mitigate the evolution of life-threatening and disabling complications of this eminently treatable condition.

#### Contributors

WG, GA, and OB were responsible for the concept and design of the guidance. OB chaired the working party. SS, TM, AS, and SV performed the literature review and synthesis of evidence. SS, TM, AS, SV, GA, AD, GTG, DK, TTW, WG, and OB were members of the writing group. VW represented the Wilson's Disease Support Group UK and was involved in the writing and review of the manuscript. All authors were responsible for the formulation of consensus recommendations and writing and critical review of the manuscript. SS and TM prepared the manuscript and figures for publication.

#### Declaration of interests

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