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ESPGHAN Guideline

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SOCIETY PAPERS

Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition

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ESPGHAN Guideline

TABLE 1. Recommendations of the ESPGHAN Hepatology Committee

1 WD should be considered in the differential diagnosis of children older than 1 year presenting with any sign of liver disease ranging from asymptomatically increased serum transaminases to cirrhosis with hepatosplenomegaly and ascites or ALF. **Grade 1A (level of agreement: 86%)**
2 WD should be ruled out in any teenager with unexplained cognitive, psychiatric, or movement disorder. **Grade 1A (96%)**
3 Diagnostic testing for WD in suspected patients should include liver function tests (serum transaminases, conjugated and total bilirubin; alkaline phosphatase and prothrombin time/INR), serum ceruloplasmin, and 24-hour urinary copper. **Grade 1A (96%)**
4 The Ferenci scoring system should be applied to children for diagnosis of WD. Mutation analysis of the *ATPB7* gene may facilitate the diagnosis. **Grade 1A (91%)**
5 Copper estimation in the liver tissue could be helpful in children where the diagnosis is uncertain. **Grade 1C (100%)**
6 Once WD diagnosis is confirmed in the proband, WD should be sought in first degree relatives including siblings, offspring, and parents by performing liver function tests, explorations of copper metabolism, and targeted molecular analysis. **Grade 1A (100%)**
7 Given its safety profile, zinc salts, preferably zinc acetate, could be used in presymptomatic children identified through family screening, or as maintenance therapy after de-coppering with chelators as long as serum transaminase levels remain normal. **Grade 2C (96%)**
8 Children with signs of significant liver disease, such as cirrhosis or abnormal INR, should be preferably treated with copper chelating agents. **Grade 2B (96%)**
9 Dietary restriction of copper-rich foods is advised until remission of symptoms and normalization of liver enzymes in children treated with copper chelating agents. **Grade 2C (82%)**
10 Children with ALF or decompensated liver cirrhosis should be transferred to and managed in pediatric liver transplantation centers. **Grade 1A (100%)**
11 Children with decompensated liver cirrhosis should be treated with a chelating agent or a combination of zinc salts and a chelating agent that may preclude the need for a liver transplantation. The King's Wilson index should be monitored for prognostic assessment and timely decision for LT. **Grade 2B (96%)**
12 Because liver transplantation corrects the enzymatic defect, chelating agents or zinc treatment is no longer required after transplantation. **Grade 1A (96%)**
13 All children should be closely followed-up during the first month following initiation of therapy, then every 1 to 3 months until remission, and every 3 to 6 months thereafter. **Grade 1C (100%)**
14 Monitoring includes physical examination, biochemical tests (ie, blood cell count, liver function tests, urea, creatinine, proteinuria), serum copper, and 24-hour urinary copper to assess efficacy, overdosage, or non-adherence to therapy and adverse events. **Grade 1C (96%)**
15 Evidence for non-adherence to zinc can be assessed by measuring serum zinc levels and/or urinary zinc/copper 24-hour excretion. **Grade 2B (91%)**
16 If increased transaminases remain or relapse despite treatment, poor compliance should be suspected. **Grade 2B (96%)**
17 The occurrence of penicillamine-related adverse events should prompt discontinuation and switching to trientine or zinc salts according to the severity of liver disease. **Grade 2B (100%)**

Voting results are indicated in brackets for each recommendation.
ALF = acute liver failure; LT = liver transplantation; WD = Wilson's disease.

Symptomatic patients with penicillamine intolerant

Adverse events:

- Hypersensitivity
- Proteinuria
- Hematologic toxicity

AASLD Guideline

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES


AASLD PRACTICE GUIDELINES

Diagnosis and Treatment of Wilson Disease: An Update

Eve A. Roberts[1] and Michael L. Schilsky[2]

Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: An update. Hepatology. 2008 Jun;47(6):2089-111.

AASLD Guideline

AASLD
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- Initial treatment for symptomatic patients.

mine or trientine and is associated with few side effects. Adequate studies regarding the timing of this change-over in treatment of adult patients with hepatic WD are not available, and only limited data are available for children.[212] No matter how well a patient appears, treatment should never be terminated indefinitely. Patients who discontinue treatment altogether risk development of intractable hepatic decompensation.[167,213]

Recommendations:

15. Initial treatment for symptomatic patients should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated (Class I, Level B).

16. Patients should avoid intake of foods and water with high concentrations of copper, especially during the first year of treatment (Class I, Level C).

17. Treatment of presymptomatic patients or those on maintenance therapy can be accomplished with a chelating agent or with zinc. Trientine may be better tolerated (Class I, Level B).

Decompensated Cirrhosis. Patients who present with decompensated chronic liver disease, typically with hypoalbuminemia, prominent coagulopathy, ascites, but no encephalopathy, have recently been treated with a chelator, either D-penicillamine[86,178] or trientine,[214] plus zinc. The two types of treatment must be temporally dispersed throughout the day in four dosages, with usually 5-6 hours between administration of either drug, in order to avoid having chelator bind the zinc and thus potentially cancel the efficacy of either modality. A typical regimen is

Scoring systems have recently been devised for children[86] and adults[216] with Wilsonian acute liver failure: both have good predictive values but do not appear to be routinely utilized. Until transplantation can be performed, plasmapheresis and hemofiltration[217] and exchange transfusion[218] or hemofiltration[219] or dialysis may protect the kidneys from copper-mediated tubular damage.[220,221] Albumin dialysis was shown to stabilize patients with acute liver failure due to WD and delay, but not eliminate, the need for transplantation.[222] The Molecular Adsorbents Recirculating System ultrafiltration device may be efficacious in this setting.[223-225]

Pregnancy. In pregnant women, treatment must be maintained throughout the course of pregnancy for all patients with WD. Interruption of treatment during pregnancy has resulted in acute liver failure.[226] Experience to date indicates the chelating agents (both penicillamine and trientine)[172,227-230] and zinc salts[231,232] have been associated with satisfactory outcomes for the mother and fetus.[36,233-237] The occurrence of a few birth defects has been noted infrequently in offspring of treated patients; however, the rarity of this disorder has made it difficult to determine whether this is different from the frequency of these defects in the population at large. The dosage of zinc salts is maintained throughout without change; however, dosages of chelating agents should be reduced to the minimum necessary during pregnancy, especially for the last trimester to promote better wound healing if cesarean section is performed. Such a dose reduction might be on the order of 25%-50% of the prepregnancy dose. Patients should be monitored frequently during pregnancy.

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- Initial treatment for symptomatic patients.
  - ✓ Less common neurological worsening
  - ✓ Effective as an initial therapy for patients with decompensated liver disease

while with overtreatment, values are very low (<5 μg/dL or <50 μg/L).

Trientine. Trientine (triethylene tetramine dihydrochloride or 2,2,2-tetramine, also known by its official short name trien) is one of a family of chelators with a polyamine-like structure chemically distinct from penicillamine. It lacks sulfhydryl groups and copper is chelated by forming a stable complex with the four constitutent nitrogens in a planar ring.

Trientine was introduced in 1969 as an alternative to penicillamine. Few data exist about the pharmacokinetics of trientine. It is poorly absorbed from the gastrointestinal tract, and what is absorbed is metabolized and inactivated.[171,172] About 1% of the administered trientine and about 8% of the biotransformed trientine metabolite, acetyltrien, ultimately appears in the urine. The acetyltrien is a less effective chelator than trientine. The amounts of urinary copper, zinc and iron increase in parallel with the amount of trientine excreted in the urine.[173]

Like penicillamine, trientine promotes copper excretion by the kidneys. Whether trientine is a weaker chelator of copper than penicillamine is controversial [160,174,175] and dose adjustments can compensate for small differences. Trientine and penicillamine may mobilize different pools of body copper.[174]

Trientine is effective treatment for WD[167,176] and is indicated especially in patients who are intolerant of penicillamine or have clinical features indicating potential intolerance (history of renal disease of any sort, congestive splenomegaly causing severe thrombocytopenia, autoim-

Neurological worsening after beginning treatment with trientine has been reported but appears much less common than with penicillamine. Trientine has also been shown to be effective initial therapy for patients, even with decompensated liver disease

trientine may cause hemorrhagic gastritis, loss of taste, and rashes.[179] Recent evidence suggests that copper deficiency induced by trientine can result in iron overload in livers of patients with WD, similar to that observed for penicillamine.[180]

Typical dosages are 750-1500 mg/day in two or three divided doses, with 750 or 1000 mg used for maintenance therapy. In children, the weight-based dose is not established, but the dose generally used is 20 mg/kg/day rounded off to the nearest 250 mg, given in two or three divided doses. Trientine should be administered 1 hour before or 2 hours after meals. Taking it closer to meals is acceptable if this ensures compliance. Trientine tablets are not stable for prolonged periods at high ambient temperatures, which is a problem for patients traveling to warm climates.

Adequacy of treatment is monitored by measuring 24-hour urinary copper excretion while on treatment. This should run in the vicinity of 200-500 μg (3-8 μmoles) per day on maintenance treatment but may be higher when treatment is first started. Additionally, estimate of non–ceruloplasmin bound copper may show normalization of the non–ceruloplasmin bound copper concentration with effective treatment.

Values of urine copper excretion below 200 μg/day (3.2 μmol/day) may indicate either nonadherence to therapy or overtreatment and excess copper removal. In those with nonadherence to therapy, non–ceruloplasmin bound copper is elevated (>15 μg/dL or >150 μg/L), whereas with overtreatment, values are very low (<5 μg/dL or <50 μg/L).

Zinc. Zinc was first used to treat WD by Schouwink in Holland in the early 1960s.[181,182] Its mechanism of action is different from that of penicillamine and trientine: zinc interferes with the uptake of copper from the

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Initial treatment for symptomatic patients.

- ✓ Less common neurological worsening
- ✓ Effective as an initial therapy for patients with decompensated liver disease

- Patients who are intolerant of penicillamine
  - ✓ Potential intolerance
    1. History of renal disease of any sort
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    3. Autoimmune tendency

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    1. History of renal disease of any sort
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    3. Autoimmune tendency

- Maintenance therapy

- Presymptomatic

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Recommendations:

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16. Patients should avoid intake of foods and water with high concentrations of copper, especially during the first year of treatment (Class I, Level C).

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EASL Guideline

Initial treatment for symptomatic patients.

Recommendation 2

- Initial treatment for symptomatic patients with Wilson's disease should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated
  GRADE II-1, B, 1
  AASLD Class I, Level B
- Zinc may have a role as a first line therapy in neurological patients
  GRADE II-2, C, 2
  AASLD Class II, Level C
- Treatment of presymptomatic patients or those with neurological disease on maintenance therapy can be accomplished with a chelating agent or with zinc
  GRADE II-1, B, 1
  AASLD Class I, Level B
- Treatment is lifelong and should not be discontinued, unless liver transplantation is performed
  GRADE II-1, B, 1
  AASLD Class I, Level B
- If zinc is used, careful monitoring of transaminases is needed, with changing to chelators if these laboratory parameters are increasing
  GRADE C1
  AASLD Class I, Level B
- Patients should avoid intake of foods and water with high concentrations of copper, especially during the first year of treatment
  GRADE II-3, B, 2
  AASLD Class I, Level C
- Patients with acute liver failure due to Wilson's disease should be treated with liver transplantation when the revised King's score is 11 or higher
  GRADE II-2, B, 1
  AASLD Class I, Level B [41]
- Patients with decompensated cirrhosis, unresponsive to chelation treatment, should be evaluated promptly for liver transplantation
  GRADE II-2, B, 1
  AASLD Class I, Level B
- Treatment for Wilson's disease should be continued during pregnancy, but dosage reduction is advisable for D-penicillamine and trientine
  GRADE II-3, B, 1
  AASLD Class I, Level C
- For routine monitoring, serum copper and ceruloplasmin, liver enzymes and international normalized ratio, functional parameters, complete blood count and urine analysis as well as physical and neurological examinations should be performed regularly, at least twice annually
  GRADE II-2, B, 1
  AASLD Class I, Level C
- The 24-hour urinary copper excretion on medication and after 2 days of cessation of therapy should be measured at least yearly. The estimated serum non-ceruloplasmin-bound copper may be another useful parameter to control therapy
  GRADE II-3, B, 1
  AASLD Class I , Level C

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European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Wilson's disease. Journal of Hepatology. 2012 Mar;56(3):671-85.

EASL Guideline

EASL™
The Home of Hepatology

Initial treatment for symptomatic patients.

Less common neurological worsening.
Patients with decompensated liver disease at the outset.

symptoms is slower and may be observed even after three years [97]. Worsening of neurologic symptoms has been reported in 10–50% of patients treated with D-penicillamine during the initial phase of treatment. In a recent series, neurologic worsening occurred on all three treatments used for Wilson's disease (D-penicillamine, trientine, zinc), but mainly with D-penicillamine, where 13.8% were adversely affected [27]. Tolerability of D-penicillamine may be enhanced by starting with incremental doses, 125–250 mg/day increased by 250 mg increments every 4–7 days to a maximum of 1000–1500 mg/day in 2–4 divided dosages. Administration of doses 1500 mg per day or higher at once may lead to rapid and often irreversible neurological deterioration. Rapid re-administration of the treatment in patients who stopped it for longer time may also evoke irreversible neurological signs.

D-penicillamine is associated with numerous side effects. Severe side effects requiring the drug to be discontinued occur in approximately 30% of patients [95,98]. Early sensitivity reactions marked by fever and cutaneous eruptions, lymphadenopathy, neutropenia or thrombocytopenia, and proteinuria may occur during the first 1–3 weeks.

Significant bone marrow toxicity includes severe thrombocytopenia or total aplasia. In these conditions, D-penicillamine should be discontinued immediately. Late reactions include nephrotoxicity, usually heralded by proteinuria or the appearance of other cellular elements in the urine, for which discontinuation of D-penicillamine should be immediate. Other late reactions include a lupus-like syndrome marked by hematuria, proteinuria, and positive antinuclear antibody, and with higher dosages of D-penicillamine no longer typically used for treating Wilson's disease, Goodpasture syndrome. Dermatological toxicities reported include progeric changes in the skin and elastosis perforans serpingosa [99], and pemphigous or pemphigoid

Typical dosages of trientine are 900–2700 mg/day in two or three divided doses, with 900–1500 mg/day used for maintenance therapy. In children, the weight-based dose is not established, but the dose generally used is 20 mg/kg/day rounded off to the nearest 250 mg, given in two or three divided doses. Trientine should be administered 1 h before or 3 h after meals. Taking it closer to meals is acceptable if this ensures compliance. Trientine tablets may not be stable for prolonged periods at high ambient temperature, which is a problem for patients travelling to warm climates.

Trientine is an effective treatment for Wilson's disease [106,107]. Trientine, while being developed for use in patients who are intolerant of penicillamine, has also been shown to be an effective initial therapy, even with patients with decompensated liver disease at the outset trientine and do not recur during prolonged treatment with

Neurological worsening after beginning of treatment with trientine has been reported but appears less common than with D-penicillamine.

of trientine and iron should be avoided because the complex with iron is toxic. A reversible sideroblastic anemia may be a consequence of overtreatment and resultant copper deficiency. Lupus-like reactions have also been reported in some Wilson's disease patients treated with trientine. However, these patients were almost all uniformly treated previously with D-penicillamine, so the true frequency of this reaction when trientine is used *de novo* is unknown.

Adequacy of treatment is monitored by measuring 24-hour urinary copper excretion (after 2 days of cessation of therapy) and by measuring non-ceruloplasmin bound copper.

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Initial treatment for symptomatic patients.

Less common neurological worsening.
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Maintenance therapy

patients with neurological disease.

Presymptomatic

Recommendation 2

- Initial treatment for symptomatic patients with Wilson's disease should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated
  GRADE II-1, B, 1
  AASLD Class I, Level B
- Zinc may have a role as a first line therapy in neurological patients
  GRADE II-2, C, 2
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- Treatment of presymptomatic patients or those with neurological disease on maintenance therapy can be accomplished with a chelating agent or with zinc
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- Treatment is lifelong and should not be discontinued, unless liver transplantation is performed
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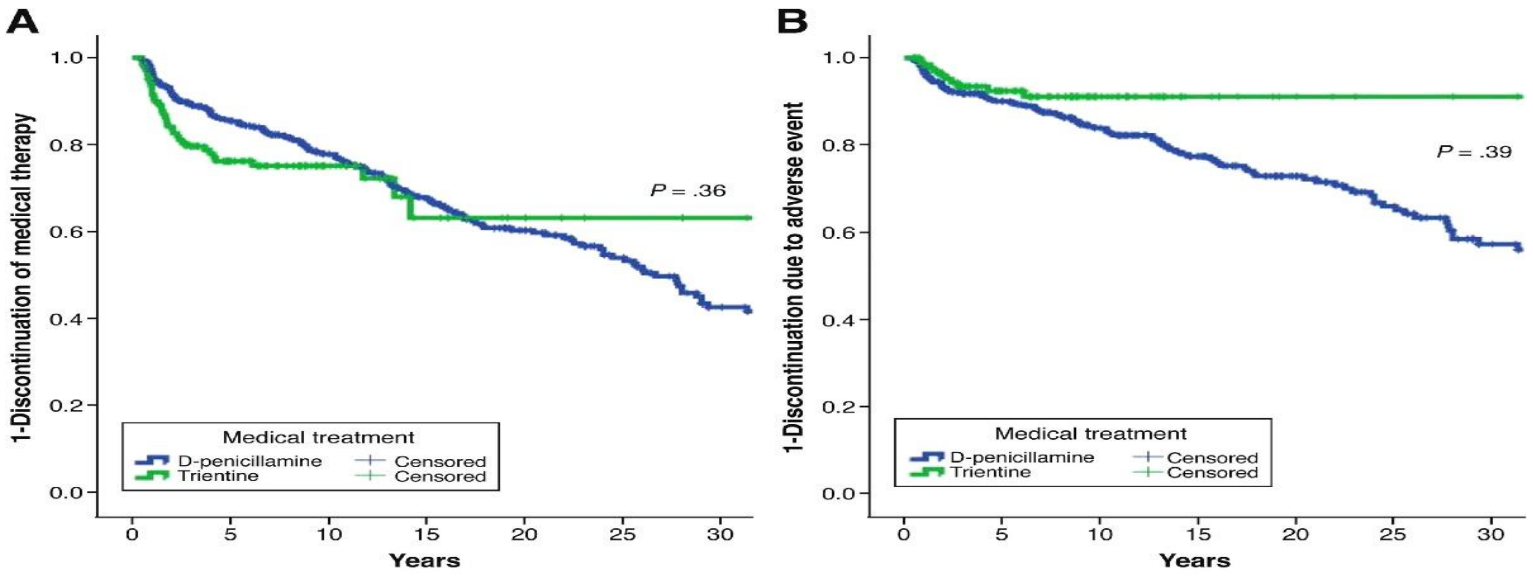
Comparison of Penicillamine and Trientine

Adverse events leading to discontinuation of treatment were more frequent among those receiving D-penicillamine than trientine.



At risk		5 years	10 years	15 years	20 years	25 years	30 years
DPA	326	254	202	150	110	79	47
Trientine	141	81	36	12	6	3	2

Discontinuation of treatments for (A) any cause or because of (B) adverse events.

Weiss KH, Thurik F, Gotthardt DN, Schäfer M, Teufel U, Wiegand F, Merle U, Ferenci-Foerster D, Maieron A, Stauber R, Zoller H, Schmidt HH, Reuner U, Hefter H, Trocello JM, Houwen RH, Ferenci P, Stremmel W; EUROWILSON Consortium. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. Clin Gastroenterol Hepatol. 2013 Aug;11(8):1028-35.e1-2.

Clinical Trial

TREATMENT OF WILSON'S DISEASE WITH TRIENTINE (TRIETHYLENE TETRAMINE) DIHYDROCHLORIDE

J. M. WALSHE

Department of Medicine, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge CB2 2QQ

Method: 20 patients with **WD** in whom **severe penicillamine intolerance** developed have been managed with the orally active chelating agent trientine dihydrochloride (trien). The stage of illness of the patients ranged from the pre symptomatic through severe neurological or hepatic disease to the "de coppered" post symptomatic cases.

Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. Lancet. 1982 Mar 20;1(8273):643-7.

Patients Characteristics

Toxic reactions to penicillamine and reasons for and timing of change to trien:

Group and patient	Penicillamine reaction	Time before toxicity	Time on penicillamine	Response to change
Group A				
1	Confluent urticaria; fever 39·4°C; haematuria; proteinuria	7 days	10 days	NR
2	Confluent urticaria; high fever; ESR 46 mm/h; malaise	7 days	2 wk	NR
3	Rash; nausea; joint pains; positive LE cells, positive ANF*	7 days	1 mo	NR
4	Severe neutropenia	3 wk	3 wk	NR
5	Rash; neutropenia	3 mo	3 mo	NR
6	Increase in symptoms of Wilson's disease; generalised joint and muscle pain	2 mo	3 mo	Recovery; NR
7	Immune-complex nephritis	6 yr‡	6 yr	NR
8	None §	0	. .	. .
Group B				
9	Bruising; thrombocytopenia; rash	1 yr	1 yr	NR
10	Thrombocytopenia; bruising	3 mo	1 yr†	NR
11	Epidermolysis bullosa	6 mo	1 yr†	NR
Group C				
12	Immune-complex nephritis	6 mo	6 mo	Recovery; NR
13	Heavy proteinuria	9 mo	9 mo	Recovery; NR
14	Immune-complex nephritis	6 mo	6 mo	Recovery; NR
15	Immune-complex nephritis	2 yr	2½ yr	Recovery; NR
16	Rheumatoid-like arthropathy; positive ANF; high ESR	6 yr	7 yr	Some improvemer
17	Severe granulocytopenia	1 yr	2 yr	Improved
18	Severe buccal ulceration	6 mo	1 yr	Healed; NR
19	Penicillamine dermatopathy	10 yr	10 yr	Skin lesions healed
20	Elastosis perforans serpigmosa	13 yr	13 yr	No improvement

ESR = erythrocyte sedimentation rate; LE = lupus erythematosus; ANF = antinuclear factor; NR = no recurrence.
*Recurred after each of three challenges with single doses.
†Intermittent.
‡This patient was without therapy for 2 years before trien was started.
§Treated with same drug as his brother (patient 9).

Efficacy

Response to trien treatment in patients with previously untreated Wilson disease

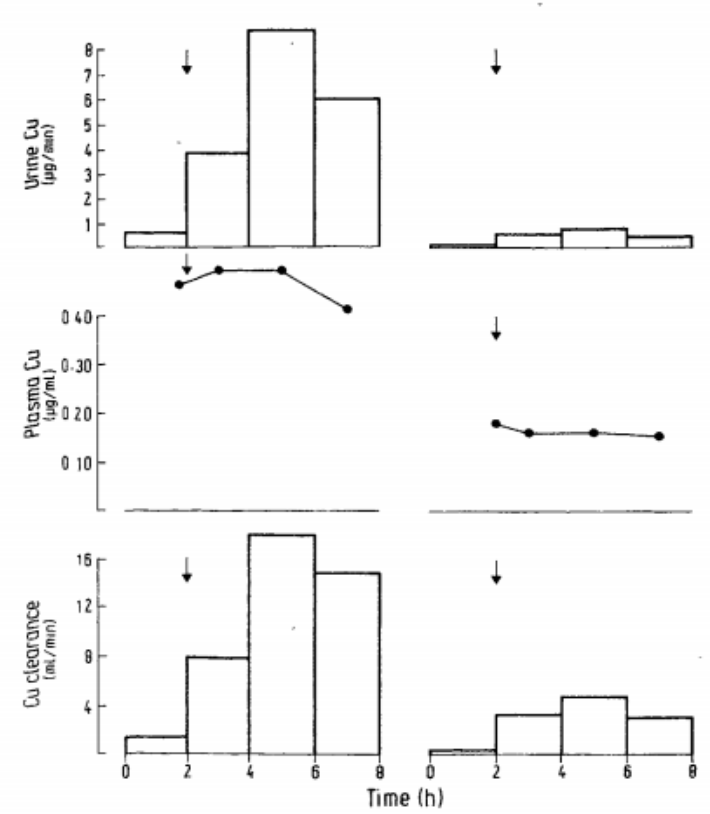
Patient	Age at onset (yr)	Age at diagnosis (yr)	Sex	KF rings (density)	Symptoms at presentation	(severity)	Time on trien (mo)	KF rings (density)	Symptoms after trien	Caeruloplasmin (mg/dl)	
										Before	After
1	13	15	M	4+	Dysarthria; drooling; tremor; ataxia*	(4+)	60	±	Dysarthria only	0	0
2	29	30	F	3+	Dysarthria; titubation; tremor; ataxia; micrographia	(3+)	40	±	None	5·3	0
3	..	27	F	+	Hepatomegaly; liver Ca 220μg/g wet weight	(0)	14	±	None	1·0	1·3
4	15	15	F	3+	Haemolytic crises; jaundice; nausea + vomiting; oedema; ascites	(3+)	24	±	None	14·0	1·5
5	20	22	F	2+	Severe titubation; tremor; ataxia; mild dysarthria; drooling	(4+)	44	0	None; two successful pregnancies	1·5	7·1†
6	13	13	M	3+	Sunflower cataracts; mild Parkinsonism; drooling	(+)	21	±	None	3·1	0
7‡	..	17	M	+	Mild intention tremor; early cogwheel rigidity	(0)	120	±	None	1·2	0
8	..	16	M	+	Slight intention tremor; abnormal liver tests	(0)	33	±	None	4·7	1·0

KF rings = Fleischer pericorneal pigment rings.
*Had splenectomy at age 11 years.
†22 weeks pregnant when estimated.
‡Previously reported.[7]

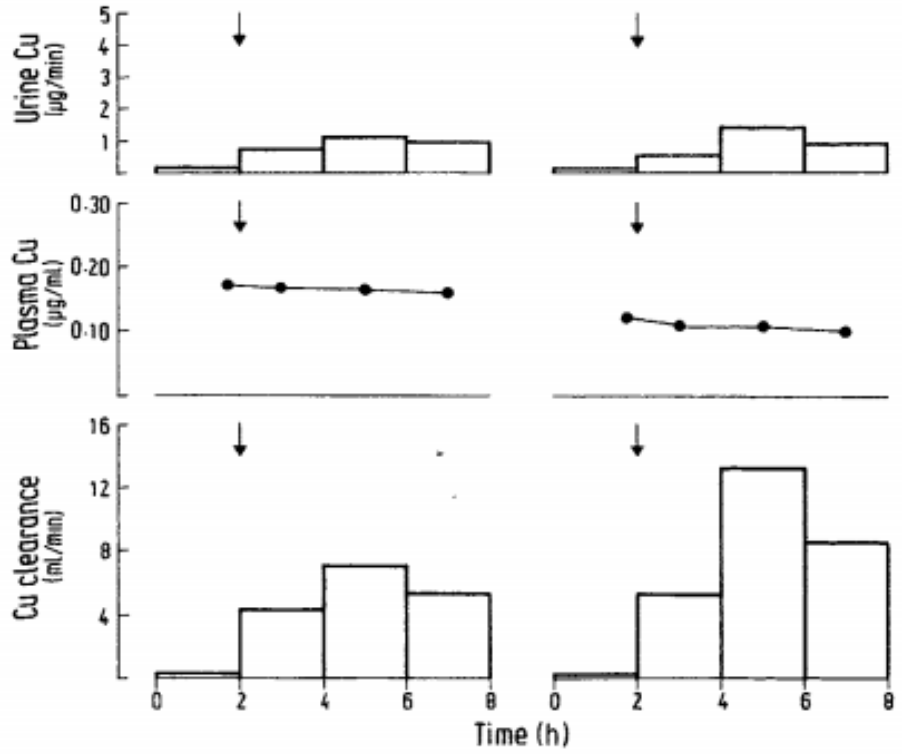
Trien is a highly effective treatment for reversing symptoms.

Efficacy

Mean of findings on patients; clearance studies before the start of treatment (left) and repeat studies 43 months (for group A) / 53 months (for group B) later (right). A single dose of trien (1200 mg) was given at 2 h (arrow).



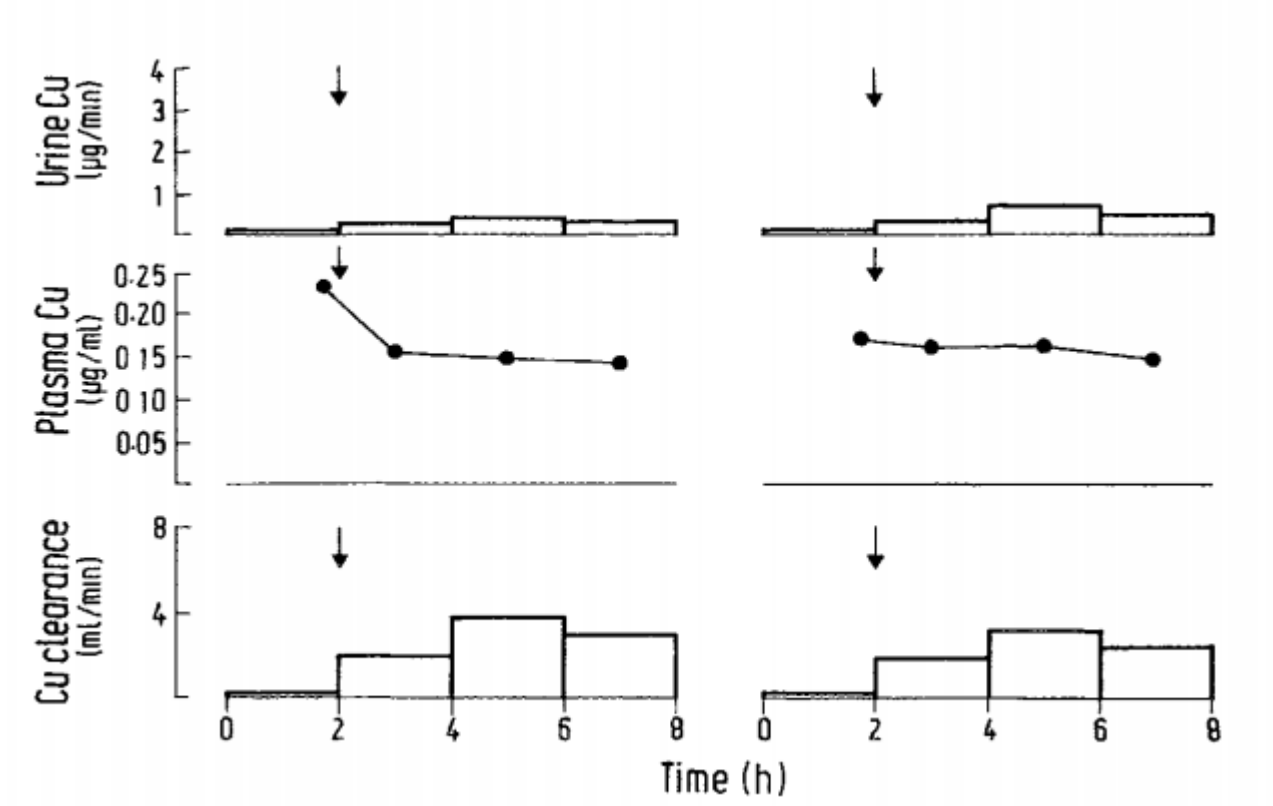
Group A



Group B

Efficacy

Mean of findings on 9 patients; clearance studies at the time of changeover to trien (left) and repeat studies 52 months later (right). A single dose of trien (1200 mg) was given at 2 h (arrow).



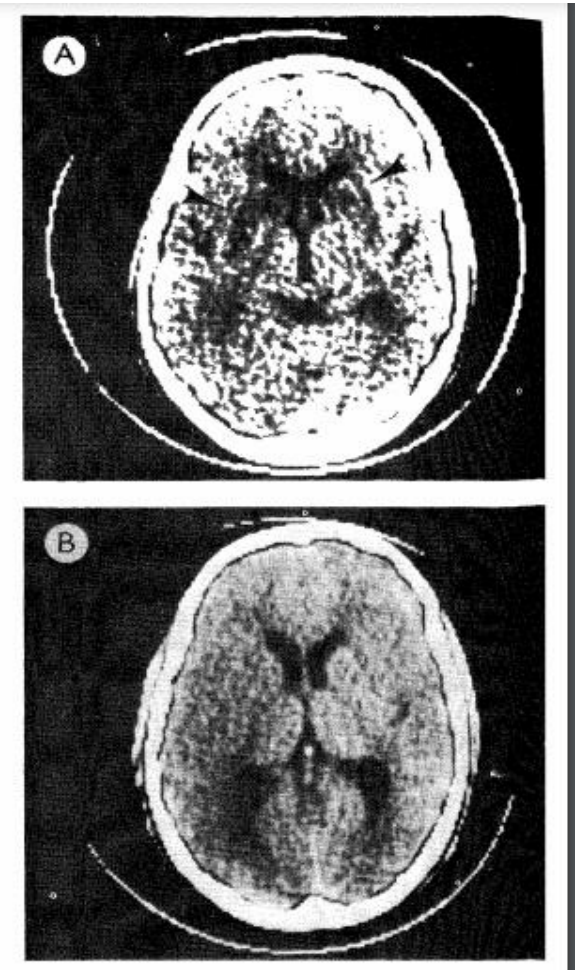
Group C

Efficacy

Computer-assisted tomography brain scans at the level of the basal ganglia from a patient with neurological Wilson's disease (patient 6).

(A) Before treatment with trien showing lucencies in the region of the basal ganglia (arrowed), left more pronounced than right.

(B) Repeat scans 18 months later. The basal-ganglial changes have resolved completely.



Safety

- In most of the patients the toxic symptoms which forced a change of therapy were reversed on trien therapy.
- Elastosis perforans did not seem to benefit, and two patients with penicillamine-induced systemic lupus erythematosus were not helped by the change.
- No other toxic signs or symptoms were observed.
- There was no evidence of teratogenicity either in animals or in the six patients who became pregnant while taking trien; all six infants have developed normally.

Conclusion

- Trien has proved to be a highly effective treatment for reversing symptoms and maintaining patients previously successfully de coppered with penicillamine.
- There has been evidence of depletion of the body stores of copper by trien coinciding with the clinical improvement.
- Trien is a satisfactory alternative therapy for Wilson's disease

Dosage Form and Formulation

- SYPPER (trientine hydrochloride) is available as 250 mg capsules (supplied in bottle of 100) for oral administration.
- Each hard capsule contains 167 mg trientine, equivalent to 250 mg trientine dihydrochloride
- White cap and body size 1.

Lexicomp. Trientine: Drug information. UpToDate Inc. https://www.uptodate.com

Patient Support Program

Dosage Form & Active Ingredient

Trientine

Active ingredient	**Trientine dihydrochloride**	**Trientine dihydrochloride**
Trientine Salt	**250 mg**	**300 mg**
Trientine Base	**167 mg**	**200 mg**
Brand Name	**Sypper**	**Zistine**