ORIGINAL CONTRIBUTION

Treatment of Wilson Disease With Ammonium Tetrathiomolybdate

IV. Comparison of Tetrathiomolybdate and Trientine in a Double-blind Study of Treatment of the Neurologic Presentation of Wilson Disease

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Objective: To compare tetrathiomolybdate and trientine in treating patients with the neurologic presentation of Wilson disease for the frequency of neurologic worsening, adverse effects, and degree of neurologic recovery.

Design: A randomized, double-blind, controlled, 2-arm study of 48 patients with the neurologic presentation of Wilson disease. Patients either received 500 mg of trientine hydrochloride 2 times per day or 20 mg of tetrathiomolybdate 3 times per day with meals and 20 mg 3 times per day between meals for 8 weeks. All patients received 50 mg of zinc 2 times per day. Patients were hospitalized for 8 weeks, with neurologic and speech function assessed weekly; discharged taking 50 mg of zinc 3 times per day, and returned annually for follow-up.

Setting: A university hospital referral setting.

Patients: Primarily newly diagnosed patients with Wilson disease presenting with neurologic symptoms who had not been treated longer than 4 weeks with an anticopper drug.

Intervention: Treatment with either trientine plus zinc or tetrathiomolybdate plus zinc.

Main Outcome Measures: Neurologic function was assessed by semiquantitative neurologic and speech examinations. Drug adverse events were evaluated by blood cell counts and biochemical measures.

Results: Six of 23 patients in the trientine arm and 1 of 25 patients in the tetrathiomolybdate arm underwent neurologic deterioration ($P<.05$). Three patients receiving tetrathiomolybdate had adverse effects of anemia and/or leukopenia, and 4 had further transaminase elevations. One patient receiving trientine had an adverse effect of anemia. Four patients receiving trientine died during follow-up, 3 having shown initial neurologic deterioration. Neurologic and speech recovery during a 3-year follow-up period were quite good.

Conclusion: Tetrathiomolybdate is a better choice than trientine for preserving neurologic function in patients who present with neurologic disease.

ClinicalTrials.gov Identifier: NCT00004339

Arch Neurol. *2006;63:521-527*

WILSON DISEASE IS AN autosomal recessive disease of a toxic reaction to copper, primarily affecting the brain and liver.[1-5] The disease is due to mutations in the *ATP7B* gene,[6-8] which produces a protein required for biliary excretion of the body's excess copper.

Three anticopper drugs are currently approved for Wilson disease. Penicillamine, a copper chelator that causes excretion of copper in the urine,[9] is effective in Wilson disease but has a long list of adverse effects.[10] Trientine hydrochloride is also a copper chelator that enhances urinary excretion of copper, is better tolerated than penicillamine,[11] and has not been evaluated in patients presenting with neurologic symptoms. Zinc, approved for maintenance therapy, induces intestinal cell metallothionein, which binds copper from food and endogenous secretions, preventing its transfer to blood,[12-14] thus producing a block of intestinal absorption of copper.

Treatment of patients initially seen with neurologic symptoms from Wilson disease has been problematic. Using a retrospective survey, we found that 50% of pa-

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Table 1. Initial Data on Participating Patients

Patient/Sex/Age	Pretreatment History	Hepatic Copper Level, µg/g	Urine Copper Level, µg/d	Ceruloplasmin Level, mg/dL
	Patients Who Received TM			
230/F/26		294	258	3.5
234/M/27				2.1
236/M/34	20 d of penicillamine	915	133	6.7
237/M/23		253	444	2.9
239/F/44		410	152	13.3
240/F/32	Recrudescence after stopped taking penicillamine			2.0
242/M/29				2.4
245/M/36		734	222	6.6
247/M/45	11 d of penicillamine	724	153	5.2
249/M/49		814	185	14.6
251/M/13		726	275	10.2
253/M/27	Recrudescence after stopped taking penicillamine		218	9.2
256/M/23	14 d of penicillamine	566	217	3.2
257/F/29	Recrudescence after stopped taking penicillamine		226	4.6
261/M/41	Recrudescence after stopped taking penicillamine		219	2.0
265/M/41		786	404	16.5
266/M/35	Recrudescence after stopped taking penicillamine		167	3.9
268/F/22	21 d of trientine	1033		10.7
271/F/39			187	11.3
273/M/32			168	12.9
274/M/23			207	1.0
275/M/42		378	360	2.0
281/M/28		508	405	8.4
282/M/31		783	234	6.0
285/M/27		727	203	2.0
Mean (SD)		643 (231)	240 (89)	6.5 (4.6)
Sample size*		15	21	25
	Patients Who Received Trientine Hydrochloride			
76/M/28		697		11.3
232/M/37			624	6.8
233/M/17				14.6
238/M/29		841	132	9.3
241/F/17		1104	155	16.1
243/F/18	21 d of penicillamine and trientine	934		2.0
248/F/25	7 d of penicillamine	953		12.5
250/F/24	7 d of trientine	1070		4.2
252/M/16		262	373	8.4
254/F/13		893		3.9
258/F/21	6 d of penicillamine		115	4.0
259/F/17			147	4.0
260/M/18				7.2
262/F/32			403	7.2
267/M/26	21 d of penicillamine			13.8
269/F/24	9 d of penicillamine			7.8
270/M/43		615	123	9.1
272/F/19		572	840	18.8
278/F/26		1112	192	2.0
279/M/34	28 d of penicillamine	857	163	2.0
280/M/37			156	3.6
284/F/13		190	166	2.0
287/M/25	7 d of penicillamine	510	187	8.7
Mean (SD)		758 (296)	270 (218)	7.8 (4.9)
Sample size†		14	14	23
Normal range		20-50	20-50	18-35

Abbreviation: TM, tetrathiomolybdate.
*Nineteen men, 6 women.
†Eleven men, 12 women.

tients presenting with neurologic symptoms treated with penicillamine had neurologic deterioration, and 77% of these were in the first weeks of therapy.[15] The likely mechanism is that during mobilization of large stores of copper in the liver, blood copper levels are elevated, causing a further elevation of copper levels in the brain. The outcome for patients who deteriorated was often very bad in that half of them never recovered to their prepenicil-

Table 2. Patients' Neurologic Scores

		Week								
	Baseline	1	2	3	4	5	6	7	8	38
24 Patients in the TM Arm Who Did Not Show Neurologic Deterioration										
Mean (SD)	7.7 (5.1)	7.4 (5.3)	7.7 (5.7)	7.5 (5.5)	7.6 (5.7)	8 (5.3)	7.2 (5.2)	5.8 (3.8)	5.1 (3.2)	
Sample size	24	16	17	21	21	21	17	14	12	
1 Patient in the TM Arm Who Showed Neurologic Deterioration										
Patient 251	7.5		7.5	9.5	13		11.5			
17 Patients in the Trientine Hydrochloride Arm Who Did Not Show Neurologic Deterioration										
Mean (SD)	8.9 (7.2)	8 (5)	8.6 (7.4)	8.5 (7.6)	9.1 (6.4)	8.1 (6.5)	8.2 (6.9)	10.0 (8.7)	9.3 (11.1)	
Sample size	17	11	12	12	15	15	15	7	5	
6 Patients in the Trientine Arm Who Showed Neurologic Deterioration										
Patient										
76	7.0	8.0	10.0	15.0	17.5	18.0	18.0	20.0		
233	10.5	12.0			18.5		19.5	20.5	22.5	
238	3.5		2.0	7.5	10.5	10.0		9.5		
243	15.0	15.0	14.0	14.0	14.0	14.5	20.5	17.0		
260	11.5	11.5	12.0	11.5	12.0	10.5	10.5		10.0	17.5
287	11.0	9.8	10.8	14.8	15.0	14.8	15.0	17.3	17.3	

Abbreviation: TM, tetrathiomolybdate.

lamine baseline and many were seriously disabled. Thus, we believe that penicillamine is contraindicated for the initial treatment of the patient with neurologic symptoms from Wilson disease. We admit that this view is not universally accepted, and some writers question the data of Brewer et al[15] and still recommend penicillamine for treating these patients. We simply point out that no one has formally and prospectively studied the risk from penicillamine-induced neurologic deterioration, and until they do, the best risk estimate is the data in Brewer et al.[15]

Zinc therapy is not the answer because it takes 4 to 6 months to control the toxic effects of copper. During this prolonged period of ongoing copper toxicity, the disease may progress on its own. Indeed, this occurred in 1 of 3 patients presenting with neurologic disease who we treated with zinc as the sole therapy.

To fill this need, we have developed a new drug, tetrathiomolybdate (TM),[16-19] which acts by forming a tripartite complex with copper and protein. Given with food, TM binds food copper and endogenously secreted copper with food proteins and prevents absorption of the complexed copper. Given without food, TM is absorbed into the blood and there complexes available copper with albumin, making the copper unavailable for cellular uptake. In a 55-patient, open-label trial of TM therapy in patients presenting with neurologic symptoms, only 2, or 3.6%, showed neurologic deterioration reaching our criteria.[19]

To evaluate the safety and efficacy of new treatments for Wilson disease in patients presenting with neurologic symptoms, we carried out a double-blind trial comparing TM and trientine, and the results are reported herein.

METHODS

The patients were diagnosed as having Wilson disease by means of standard criteria previously published. Selected diagnostic data are presented in **Table 1**. In addition to the underlying diagnosis of Wilson disease, all patients were diagnosed as having symptoms of a movement disorder attributable to Wilson disease. If patients had received treatment for longer than 28 days with penicillamine or trientine, they were excluded. Most patients were newly diagnosed, but a few were accepted who had been receiving long-term treatment with penicillamine, stopped their therapy more than 1 year prior to consideration, and then developed new neurologic symptoms. Pretreatment history is given in Table 1. The institutional review board of the University of Michigan Medical School, Ann Arbor, reviewed and approved the project.

Each patient was admitted for 8 weeks in the General Clinical Research Center of the University of Michigan Hospital, Ann Arbor. After initial studies to confirm the diagnosis, obtain informed consent, and establish baseline neurologic and speech function, patients were randomized to 1 of 2 treatment arms using a table of random numbers. In arm 1, patients received TM in doses of 20 mg 3 times daily with meals and 20 mg 3 times daily between meals. In arm 2, patients received 500 mg of trientine hydrochloride 2 times daily between meals. Tetrathiomolybdate and trientine were placed in identical-appearing capsules. Matching placebo capsules were used so that all patients received the same number of doses at the same time. All patients received 50 mg of zinc 2 times daily.

Criteria for adverse effects included anemia (a replicable hemoglobin value $< 80\%$ of baseline), leukopenia (a replicable white blood cell count $< 80\%$ of baseline), and transaminase elevations consisting of a replicable quadrupling of baseline values of either aspartate aminotransferase or alanine aminotransferase. In the event of anemia or leukopenia, a drug holiday was given until recovery, then the drug treatment was restarted at half levels. A subsequent drop of 20% of the blood value involved resulted in discontinuation of the drug treatment. A quadrupling of transaminase values resulted in discontinuation of the drug regimen.

During the 8-week hospital admission, a quantitative neurologic test and a quantitative speech test were carried out at weekly intervals. These methods have been previously published and are standardized for and previously evaluated in Wilson disease.[19] The neurologists and speech pathologist were

Table 3. Patients' Speech Scores

	Baseline	Week 1	2	3	4	5	6	7	8	38
24 Patients in the TM Arm Who Did Not Show Neurologic Deterioration										
Mean (SD)	3.1 (1.6)	3.3 (1.6)	3.3 (1.6)	3.3 (1.8)	3.0 (1.7)	3.2 (1.6)	2.8 (1.6)	3.3 (1.5)	3.0 (2.0)	
Sample size	24	18	20	16	20	22	14	16	15	
1 Patient in the TM Arm Who Showed Neurologic Deterioration										
Patient 251	5.0	5.0	5.0	5.5	6.0	6.0				
17 Patients in the Trientine Hydrochloride Arm Who Did Not Show Neurologic Deterioration										
Mean (SD)	3.6 (1.6)	3.6 (1.6)	3.5 (1.4)	3.9 (1.3)	3.7 (1.8)	3.8 (1.8)	3.6 (1.7)	3.3 (1.7)	3.6 (2.4)	
Sample size	17	15	13	15	13	12	15	13	4	
6 Patients in the Trientine Arm Who Showed Neurologic Deterioration										
Patient										
76	5.0	6.0	5.0	5.5	5.0			4.5	4.5	
233	4.5		5.0	6.0		5.5	5.5	5.5	5.5	
238	4.0	3.0	3.0	4.0	3.0	4.5		4.0		
243	5.0	5.0	4.5	4.5	4.5	5.5	5.5	6.0	4.5	
260	4.0	3.5	3.5	4.0	4.0	4.0	4.0		4.0	6.0
287	5.0	4.5	6.0	5.5		7.0	6.0	5.0		

Abbreviation: TM, tetrathiomolybdate.

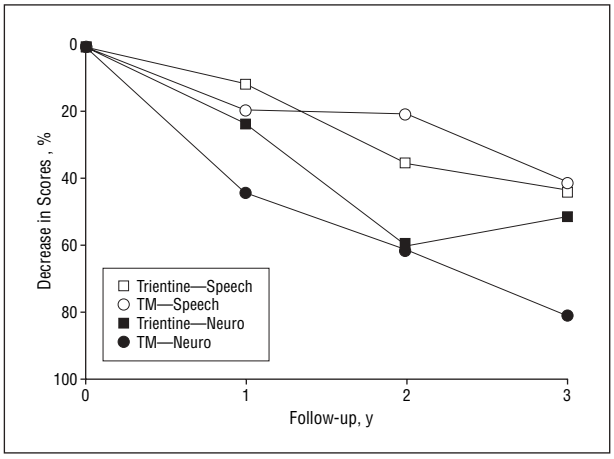

Figure. The improvements in neurologic scores (neuro) and speech scores (speech) during years of follow-up in patients treated with tetrathiomolybdate (TM) and trientine.

blinded. A replicable increase of 5 points (scale, 0-38) on the quantitative neurologic examination or a replicable increase of 3 points (scale, 0-7) on the speech examination was taken as evidence of significant neurologic deterioration. The patients were discharged from the hospital taking a regimen of zinc maintenance therapy and then returned for annual visits for 3 years, with repeat studies of the neurologic and speech examinations.

During the 8-week admission, assays of safety variables were carried out. These included complete blood cell counts; liver function tests; blood levels of amylase, lipase, creatinine, urea nitrogen, uric acid, and iron variables; and urine protein levels, all carried out by standard techniques in use at the University of Michigan Health System hematologic and biochemistry laboratories. Blood ceruloplasmin was also assayed in these laboratories.

Urine was collected for copper measurements in acid-washed, trace element–free containers, and urine and serum copper levels were measured by atomic absorption. Nonceruloplasmin plasma copper (sometimes called "free" copper) levels were determined by subtracting 3 μg for every 1 mg/dL of ceruloplasmin from the serum copper, expressed as microgram per deciliter.

RESULTS

The average neurologic scores for the patients who did not deteriorate in the TM arm during the 8-week admission and the individual weekly scores for the single patient who reached criteria for neurologic deterioration are presented in **Table 2**. The average neurologic scores for the patients who did not deteriorate in the trientine arm during the 8-week admission are also presented in Table 2. Five patients reached criteria for neurologic deterioration during the 8 weeks, and a sixth (patient 260) was reported by his family to have deteriorated significantly shortly after discharge to his home in Venezuela. On readmission 9.5 months after his initial hospital admission, he was found to have reached criteria for worsening in spite of evidence of good compliance with maintenance therapy. The individual weekly scores for these 6 patients are presented at the bottom of Table 2. A careful review of plasma copper, urine copper, and nonceruloplasmin plasma copper levels found very similar results in the patients who deteriorated compared with those who did not deteriorate (data not shown).

Neurologic deterioration in 6 of 23 patients in the trientine arm compared with 1 of the 25 patients in the TM arm was statistically significant ($P<.05$). The baseline neurologic scores of all 48 patients averaged about 8.4 and was not significantly different between the 2 arms. The mean baseline neurologic scores of the patients who worsened was 9.5, not significantly different than the whole sample.

The average speech scores for the patients who did not deteriorate neurologically in the TM arm during the 8-week admission are presented in **Table 3**, along with individual weekly scores for the 1 patient who deteriorated neurologically. The average speech scores for the patients who did not deteriorate neurologically in the trientine arm during the 8-week admission are also pre-

Table 4. Adverse Effects From Anticopper Drugs in the 48 Patients

Treatment Arm	Patient	Hemoglobin Level, g/dL		White Blood Cell Count, $\times 10^3/\mu L$	
		Baseline	At Criteria	Baseline	At Criteria
		Anemia/Leukopenia			
Trientine hydrochloride	252	13.1	11.1	3.9	2.8*
TM	230	12.8	8.9*	3.0	1.5*
	265	13.7	11.2	3.9	1.9*
	274	13.4	10.8*	2.2	2.1

Treatment Arm	Patient	AST Level, U/L		ALT Level, U/L	
		Baseline	At Criteria	Baseline	At Criteria
		Transaminase Elevations†			
TM	237	24	72	28	320*
	240	23	96*	35	333*
	242	55	168	46	504*
	281	23	72	27	240*

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TM, tetrathiomolybdate.
*Indicates criterion being reached.
†No patients were taking trientine.

sented in Table 3, along with individual weekly scores for the 6 patients who deteriorated neurologically. No patient in either arm reached criteria for speech deterioration, although 5 of the 7 patients who deteriorated neurologically showed some worsening in speech score.

Baseline speech scores of the patients who did not deteriorate neurologically averaged 3.32, and the baseline speech scores of the 7 patients who deteriorated neurologically averaged 4.64 and were significantly higher ($P<.04$). This suggests that a high baseline speech score is predictive of neurologic deterioration during treatment. In fact, none of 25 patients with a baseline speech score of 3.5 or less deteriorated, while 7 of 24 patients with baseline scores of 4.0 or higher deteriorated.

Long-term neurologic recovery was quite good in those patients who returned for follow-up. During a 3-year period, patients initially treated with TM recovered an average of 81% of their neurologic function and patients treated with trientine, 51% (**Figure**). The lower value for the trientine arm at 3 years is probably a sampling artifact from the particular patients who returned at 3 years because at 2 years, TM- and trientine-treated patients were equivalent at about 60%. Recovery of speech function also occurred (Figure) but not to the same degree as neurologic recovery on a percentage basis.

During the 8 weeks of drug therapy, 3 patients in the TM arm and 1 patient in the trientine arm reached criteria for anemia and/or leukopenia, while 4 patients in the TM arm and zero patients in the trientine arm reached criteria for transaminase elevations (**Table 4**). A careful review of copper and molybdenum data on the patients receiving TM found very similar results for the plasma copper, urine copper, nonceruloplasmin plasma copper, and urine molybdenum levels in the patients showing adverse effects compared with those who did not. However, the plasma molybdenum level was significantly higher during the first 2 weeks of therapy in those who showed adverse effects. This difference is unexplained but may be related to the TM-produced adverse effects. There were no negative effects on other safety variables with either drug.

Table 5. Deaths in the 48 Patients

Treatment Arm	Patient	Months Until Death	Cause of Death
Trientine hydrochloride	233	22	Severe neurologic impairment, general inanition, infection
	260	11.5	Neurologic deterioration beginning soon after hospital discharge, general inanition
	280	12	Severe neurologic impairment initially, no improvement, general inanition
	287	6	Severe neurologic impairment, pulmonary congestion
TM	249	14	Severe neurologic impairment initially, no improvement, late neurologic worsening, general inanition
	251	17.5	Leukemia

Abbreviation: TM, tetrathiomolybdate.

Two patients in the TM arm died during follow-up (**Table 5**). One of these was the patient who had neurologic deterioration (patient 251). However, he died of leukemia presumably unrelated to Wilson disease or its therapy. Four patients in the trientine arm died during follow-up (Table 5). Three of these (patients 233, 260, and 287) were patients who deteriorated neurologically while receiving trientine therapy.

Values for 24-hour urine copper and nonceruloplasmin plasma copper initially, at 7 to 8 weeks, and at 1 year are given in **Table 6**. The 7- to 8-week value for urine copper for trientine-treated patients reflects the effect of the drug on urinary copper excretion. Urine copper values at 1 year show that the urine copper has come under good

Table 6. 24-Hour Urine Copper and Nonceruloplasmin Plasma Copper Values*

	TM			Trientine Hydrochloride		
	Initial	7-8 wk	1 y	Initial	7-8 wk	1 y
24-h urine copper level, µg	240 (20)	213 (23)	89 (10)	270 (60)	1102 (50)	116 (30)
Nonceruloplasmin plasma copper level, µg/dL	17.2 (2.3)	11.8 (4.3)	7.4 (1.7)	10.7 (2.2)	11.8 (3.6)	7.3 (1.5)

Abbreviation: TM, tetrathiomolybdate.
*Values are expressed as mean (SE).

Table 7. Liver Function Test Values*

	TM			Trientine Hydrochloride		
	Initial	7-8 wk	1 y	Initial	7-8 wk	1 y
Albumin level, g/dL	4.0 (0.1)	3.4 (0.1)	3.7 (0.14)	3.0 (0.1)	3.2 (0.1)	3.8 (0.12)
AST level, U/L	48.1 (12.4)	62.5 (20)	34.0 (2.45)	42.9 (5.1)	41.2 (5.1)	34.1 (3.2)
ALT level, U/L	55.5 (13.7)	64.1 (8.8)	45.2 (4.25)	44.2 (3.9)	62.4 (19.9)	50.4 (5.4)
Bilirubin level, mg/dL	1.17 (0.19)	0.74 (0.09)	0.7 (0.09)	1.03 (0.11)	0.64 (0.06)	0.7 (0.12)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TM, tetrathiomolybdate.
SI conversion factor: To convert bilirubin to micromoles per liter, multiply by 17.1.
*Values are expressed as mean (SE).

control (while the normal value is ≤50 µg, values lower than 125 µg are viewed as under good control).[13] The normal value for nonceruloplasmin plasma copper is about 10 ug/dL, so the values at 1 year show good control.

Results of liver function tests initially, at 7 to 8 weeks, and at 1 year are presented in **Table 7**. The serum albumin value was lower than normal in 10 of 25 patients in the TM arm initially, and this had declined to 6 of 18 at 1 year. For the trientine arm, the serum albumin value was lower than normal in 9 of 23 patients initially and declined to 3 of 14 at 1 year. Mean aspartate aminotransferase and alanine aminotransferase levels tended to decline over 1 year. At 1 year, aspartate aminotransferase values were higher than normal (35 U/L is the upper limit of normal) in 5 of 18 patients in the TM arm and in 6 of 14 patients in the trientine arm. At 1 year, alanine aminotransferase values were higher than normal (45 U/L is the upper limit of normal) in 10 of 18 patients in the TM arm and in 10 of 14 patients in the trientine arm. Continued mild elevations of these enzymes are quite common in patients with Wilson disease receiving maintenance therapy. Regarding total bilirubin level, 9 of 25 patients in the TM arm showed values higher than normal (1.1 mg/dL), initially, and this was reduced to 3 of 22 at 1 year. In the trientine arm, 7 of 23 patients showed values higher than normal initially, and this was reduced to none of 19 at 1 year.

COMMENT

In this study, trientine, used as initial therapy for patients with neurologic symptoms of Wilson disease, showed a 26% risk (6 of 23 patients) of being associated with neurologic deterioration. Tetrathiomolybdate showed a 4.0% risk (1 of 25 patients) of being associated with neurologic deterioration, almost exactly the same risk seen in our open study of TM (3.6% [2/55]). The difference in risk between trientine and TM in the current study is statistically significant ($P<.05$).

Long-term neurologic recovery overall was very good (Figure). Speech recovery was fair and did not differ between the 2 arms. Trientine was well tolerated. Only 1 patient developed anemia/leukopenia. Tetrathiomolybdate showed a frequency of about 12% of anemia and/or leukopenia (3 of 25 patients) and about 16% of transaminase elevations (4 of 25 patients). These problems were easily handled by dose reduction and/or drug holiday. The frequency of these problems with the 120-mg dose of TM given for 8 weeks has led to a new trial of 120 mg of TM for 2 weeks followed by 60 mg for 14 weeks, which is currently ongoing.

This study suggests that neurologic deterioration during initial treatment with trientine is a grave prognostic sign. Of the 6 patients treated with trientine who deteriorated, 3 died. Of the other 17 patients who did not deteriorate, only 1 died. Two of the 3 patients treated with trientine who deteriorated but did not die ended up with severe, permanent neurologic impairment. One of these ended up much worse than his baseline, and one ended up about the same as baseline. One patient treated with trientine who had neurologic deterioration ended up doing well, but this patient is the only 1 of 6 patients treated with trientine who deteriorated initially and did well in the end.

These data indicate that TM, given together with zinc, is the preferred treatment over penicillamine and trientine for the neurologic presentation of Wilson disease. A direct comparison of TM and zinc has not been done and could be considered. It has been our view that zinc is too slow acting and the disease may progress during the first 6 months of zinc therapy, and indeed, this happened in 1 of 3 patients we treated with zinc

prior to TM availability. With the present dosage regimen of TM, patients should be followed up weekly, particularly beginning at week 3, for anemia and/or leukopenia or transaminase elevations. If one of these occurs, the drug should be temporarily stopped and after a few days, resumed at half dose. Tetrathiomolybdate is still an experimental drug. It should become available commercially in the next year.

Accepted for Publication: December 2, 2005.
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Funding/Support: This work was supported by grant FD-U-000505 from the US Food and Drug Administration's Orphan Products Office and by the General Clinical Research Center of the University of Michigan Hospitals, which is supported by grant MO1-RR00042 from the National Institutes of Health.
Financial Disclosure: The University of Michigan has recently licensed the antifibrotic and anti-inflammatory usesof tetrathiomolybdate to Pipex, Inc, Miami, Fla. Dr Brewer has equity in and is a consultant to Pipex, Inc.

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Announcement

Online Submission and Peer Review System Available. The *Archives of Neurology* editorial office has introduced an online manuscript submission and peer review system developed by eJournalPress that will serve the needs of authors, reviewers, and editors. The new system went live on November 14, 2005. See http://archneur.ama-assn.org for more detailed information.