

DRAFT FOR CONSULTATION

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
<p>Ambrose.M.L., Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. <i>Alcoholism, Clinical and Experimental Research.</i> 2001; 25(1):112-116. Ref ID: 2055</p>	<p>1+ RCT</p> <p>Randomised, Double blinded,</p> <p>Drop out: 43/169 (25%)</p>	<p>N = 169</p> <p>Reported results n=107</p>	<p>Inclusion criteria: Recruited from consecutive admissions to 12 bed detoxification unit. All conformed to a DSM-IV diagnosis of alcohol dependence but did not have the triad of acute symptoms of Wernicke-Korsakoff syndrome (WKS)</p> <p>Patient Characteristics: Mean age = 42 years Sex = not specified They had been drinking for an average 17 years. No difference in number of neurological signs between groups (ataxia, eye signs, and reduced consciousness) no significant difference in pre-trial MMSE in all 5 groups</p> <p>NB. The final treatment groups differed in age and average daily ethanol consumption. Therefore data from 19 participants were removed to equate treatment group means on the background variables of age, education, and drinking history. The authors do not make clear how the 19 cases were selected, although they comment that this was done without regard to treatment outcome data.</p>	<p>Participants were randomly assigned to 1 of 5 treatment regimes:</p> <ol style="list-style-type: none"> 1. 5 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days n=20 2. 20 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days n=24 3. 50 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days n=21 4. 100 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days n=24 5. 200 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days n=18 <p>Participants were randomized as they</p>	<p>See intervention</p>	<p>3 days</p>	<p>Test of working memory (delayed alternation task) - assessed by psychologist blind to treatment groups.</p> <p>Delayed alternation task: the participant had to correctly identify under which of 2 covers a coin was placed. The coin was moved according to a set pattern. The learning criterion was reached after 12 consecutive correct responses.</p>	<p>Australian Postgraduate Research Award, Australian National Health and Medical Research Council grant</p>

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				began a 4-5 day alcohol withdrawal regime. All subjects were administered a reducing schedule of oral diazepam				
<p>Effect Size Outcomes Learning and Memory (delayed alternation task):</p> <ul style="list-style-type: none"> • There was a significant difference between dosage groups in the number of trials taken to reach the alternation task criterion, $p=0.047$, with 50 mg treatment group needing the fewest trials (38) to reach the criterion and the 20mg treatment group needing the most (56). • A comparison between the 200mg treatment group and the mean of the other dosage groups was significant, $p=0.031$ • Although the 50mg treatment group appeared to require fewer trials, post-hoc comparisons made between the 50mg group and the other treatment groups were non-significant: 5 vs. 50 mg $p=0.166$; 20 vs. 50mg $p=0.043$; 100 vs. 50mg $p=0.090$; 200 vs. 50mg $p=0.561$ <p>Authors' conclusion: <i>'in view of the relatively small sample size of each treatment group, the high rate of non-completion, and the short duration of thiamine treatment, our results should be regarded as preliminary.'</i></p>								
Wood B, Currie J, Breen K. Wernicke's encephalopathy in a metropolitan hospital. A prospective study of incidence, characteristics	3 prospective case series	N=32	Inclusion criteria: patients admitted over a 33 month period with a diagnosis of acute Wernicke's encephalopathy (WE). A diagnosis of WE was recorded if ophthalmoplegia was present with at least 2 of 3 other features- nystagmus, ataxia and global confusional state. Patients were then examined thoroughly according to a more detailed protocol. Patient Characteristics:	Thiamin hydrochloride - administered after initial examination - first dose intravenous - then given intramuscularly for 1 week - all other vitamins were withheld for 1 week - after 1 week, patients received thiamine and	NA	6-18 months	Thiamine status, gross nutritional state, biochemical response to treatment, Korsakoff's psychosis, clinical features.	Australian Associated Brewers

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and outcome. <i>Medical Journal of Australia.</i> 1986; 144(1):12-16. Ref ID: 195			Alcoholism: all patients Male/female: 28/4 Mean age: 51.1 (SD 10.6 yrs) Ingested >120g ethanol/day in the form of beer: 21/27 (66%) Duration of excessive drinking: only known in 14 patients: 23 yrs (SD 11yrs)	multi-vitamin by mouth.				

Effect Size

Outcomes

Clinical characteristics in 32 patients on admission and discharge:

	On admission	At discharge	P value
Ophthalmoplegia	30/32 (94%)	2/32 (13%)	p<0.001
Nystagmus	29/32 (91%)	26/32 (81%)	-
Long-term memory deficit	28/31 (90%)	18/31 (58%)	p<0.01
Short-term memory deficit	30/30 (100%)	24/29 (83%)	p<0.05
<i>Peripheral neuropathy:</i>			
Muscle weakness	16/31 (51%)	6/30 (20%)	p<0.05
Reflex impairment	30/32 (94%)	27/30 (90%)	-
Sensory impairment	22/31 (71%)	17/30 (57%)	-

Clinical characteristics in 27 patients at discharge and at last visit:

	At discharge	At last visit	P value
Ophthalmoplegia	4/22 (15%)	2/27 (15%)	-

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	Nystagmus	22/27 (82%)	21/27 (78%)	-				
	Long-term memory deficit	14/26 (54%)	21/26 (81%)	p<0.05				
	Short-term memory deficit	17/24 (71%)	24/26 (92%)	-				
	<i>Peripheral neuropathy:</i>							
	Muscle weakness	5/25 (20%)	3/24 (13%)	-				
	Reflex impairment	23/25 (92%)	21/25 (92%)	-				
	Sensory impairment	12/25 (48%)	10/25 (40%)	-				
	<i>Korsakoff's psychosis</i>	14/27 (52%)	16/26 (52%)	-				

Mortality:

- At long term follow up (5 lost) 2/ 27 (7%) patients died and 3 others could not be located

Wood B, Currie J. Presentation of acute Wernicke's encephalopathy and treatment with thiamine. *Metabolic Brain Disease*. 1995; 10(1):57-72. Ref ID: 2045 – further results:

1. Ophthalmoplegia:

- The rate of improvement was affected by the severity of liver disease, p<0.001 and by the severity of fatty liver, p<0.001
- Subjects with no fatty liver had the fastest improvement in ophthalmoplegia to treatment, but all subjects reached the same level by the end of 14 days.

2. Nystagmus:

- Scores for individual tests of nystagmus all showed improvement, p<0.01
- At discharge only 6 subjects were completely free of nystagmus.

3. Global confusion state:

- The state of consciousness rapidly improved within hours of thiamine treatment, p<0.001 and continued to improve slowly, p<0.02
- The severity of disorientation in time improved over time, p<0.001, but improvement slowed by 7 days, p<0.05, and thereafter, p<0.01.
- By discharge, most subjects were still disorientated in time and 18 patients still did not know the day of the week.

4. Global severity of Wernicke's Encephalopathy:

Global severity of acute Wernicke's	Admission	Discharge
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Class 4: ophthalmoplegia, ataxia +/- confusion			3	0				
Class 3: ophthalmoplegia, nystagmus, ataxia +/- confusion			27	4 (a)				
Class 2: nystagmus, ataxia +/- confusion			2 (b)	22				
Class 1: nystagmus, +/- confusion			0	0				
Class 0: complete absence of these features			0	6				
<p>(a)- residual ophthalmoplegia only (b)- one case was subsequently found to have received thiamine just prior to assessment.</p> <p>Authors' Conclusion: <i>'the overall setting for Wernicke's encephalopathy in this study thus appears to be chronic, severe alcohol abuse accompanied by cerebral atrophy and liver disease but often without gross evidence of malnutrition. These features, together with an imperfect correlation with thiamine deficiency and an incomplete resolution of most clinical signs (other than ophthalmoplegia) suggest that circumstances other than simple thiamine deficiency contribute to brain damage in these patients.'</i></p>								
Victor M, Adams RD, Collins GH. <i>The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations.</i> Philadelphia: F A Davis; 1971. Ref ID: 2052	2 - case-control	N= 245 (case series) N=51 (nutritional case-control study)	Inclusion criteria (for main case series): patients, practically all alcoholics (all but 2), who presented with wernicke's encephalopathy or Korsakoff's psychosis or both. Exclusion criteria: not reported Patient characteristics for main case series): Age range: 20-79 Male: female: 154/91	Cases N=22 Given 1 of 3 dietary regimes: 1) a solution containing 200gm, glucose and 1.3 gm sodium chloride per litre of water (n=9)- up to 11 days 2) the unfortified rice diet of Kempner (rice, fruit, fruit juices, sugar and honey) (n=27) up to 14 days 3) the vitamin B diet	Controls N=29 Closely observed while they were receiving a full diet and all vitamin supplements	Up to 10 years (case series)	Reduction in symptoms	Not reported

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<p>Baines M, Bligh JG, Madden JS. Tissue thiamin levels of hospitalised alcoholics before and after oral or parenteral vitamins. <i>Alcohol & Alcoholism</i>. 1988; 23(1):49-52.</p>	<p>1+ RCT Randomized, Blinding and allocation concealment unclear.</p>	<p>N=25</p>	<p>Inclusion criteria: patients admitted to a special unit for treatment of alcohol dependence, drinking up to the day of admission but not requiring urgent medical treatment and showing the capacity for rehabilitation. Exclusion criteria: patients who had clinical features suggestive of brain damage, malabsorption or vitamin deficiency. Patient Characteristics: Male/female: 16/9 Mean age (range): 38.9 years (22-62) The groups were similar in their sex and age distribution (no figures provided).</p>	<p>Multivitamin supplementation containing 250mg thiamine by single i.m. injection for 5 days N=8 All groups were offered a normal hospital diet and received chlordiazepoxide as part of their withdrawal treatment.</p>	<p>1) Oral multivitamin supplementation containing 50mg thiamin 5 times daily for 5 days N=8 2) control group who received no vitamins N=9</p>	<p>7 days</p>	<p>Erythrocyte thiamine diphosphate (TDP) (measure of the physiologically active form of thiamine in tissue)</p>	<p>Counts of Chester Hospital (supplied the multivitamins)</p>
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Effect Size**The response of erythrocyte TDP level**

(Normal reference range for TDP level 165-286 nmol/l)

	Mean (\pm S.D.) Erythrocyte TDP (nmol/l)		
	None (n=9)	Oral (n=8)	Parenteral (n=8)
Day 0 (pre-treatment)	218 (\pm 29)	218 (\pm 27)	207 (\pm 47)
Day 1 (post 250mg thiamine orally or parenterally)	209 (\pm 39)	265* (\pm 51)	328† (\pm 117)
Day 7 (post 5 \times 250mg thiamine as above)	220 (\pm 56)	308† (\pm 64)	298† (\pm 75)
Change in mean after 250mg thiamin, or control	-9	+47	+121
Change in mean after 5 \times 250mg thiamine or control	+2	+90	+91

* $p < 0.1$ † $p < 0.05$

Authors' Conclusion: 'for urgent repletion of thiamine stores, therefore, as in the Wernickes-Korsakoff syndrome, the parenteral route is indicated. However, after 250mg daily for 5 days both treatment groups showed a significant ($p < 0.05$) and almost identical mean increase in their erythrocyte TDP level indicating that in those patients not requiring urgent repletion the oral route would achieve the same result as the parenteral.'

Limitations:

- There is seems to be some debate over the most accurate measure of tissue thiamin level, with previous studies reporting erythrocyte enzyme transketolase (ETKA) rather than TDP. This may affect the final results.
- This study excluded patients with vitamin deficiencies, which may be an important group of patients in which thiamin is used.

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<p>Brown LM, Rowe AE, RYLE PR et al. Efficacy of Vitamin Supplementation in Chronic Alcoholics undergoing Detoxification. Alcohol & Alcoholism. 1983; 18(2):157-166.</p>	<p>2+ non-randomized trial</p>	<p>N=97 N=73 completed trial</p>	<p>Inclusion criteria: patients admitted to the detoxification unit who had not taken vitamin preparations within one month of admission and who had no signs of Wernicke’s encephalopathy. All patients had been drinking in excess of 150cl of alcohol per day and were chemically dependent. Exclusion criteria: see above Patient Characteristics: Analyses showed no significant difference between the patient groups in respect to age, sex or social stability (no data provided)</p>	<p>Group A: Parentrovite i.v. HP 10ml daily for 5 days (1 dose of parentrovite contains 250mg thiamine HCl) N=26 By day 5 they had received a total of 1250mg of thiamine i.v. All patients received 100mg thiamine HCl i.v. on admission because of the acknowledged risk of Wernicke’s encephalopathy. All patients were involved in the normal detoxification process, which involved giving chlormethiazole and other appropriate drugs intended to reduce the serious complications such as fits and DTs.</p>	<p>Group B: oral orovite 1 tablet 3 times a day for 5 days. (3 tablets of orovite contains 150mg thiamine) By day 5 they had received 750mg of oral thiamine and 100mg i.v N=24 Group C: placebo given 3 times per day for 5 days. N=23 See intervention for more details</p>	<p>5 days</p>	<p>Thiamine, riboflavin, pyridoxine status (via erythrocyte transketolase (ETK), glutathione reductase (EGR) and glutamate-oxaloacetate transaminase (EGOT)- the effect of vitamin supplementation in improving enzyme activity in systems where specific vitamins are known to act as co-factors)</p>	<p>Not reported</p>
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Effect Size

Response of ETK activity to vitamin supplementation

Group (n)	Day 0			Day 2			Day 5		
	Mean	SD	Normals	Mean	SD	Normals	Mean	SD	Normals
Gp A (26) i.v.	66.2	14.5	10	68.7*	14.0	10	75.5**	12.9	12
Gp B (24) oral	65.9	13.9	8	70.0*	12.5	8	76.8**	11.4	15
Gp C (23) Placebo	67.9	14.2	8	68.4	13.8	11	75.8**	15.2	15
Totals (73)	-	-	26	-	-	29	-	-	42

The significant differences (within each group) from the previous mean are indicated at the 95% (*) and 99.9% (**) confidence levels. The number of normals is the number of patients inside the normal range of ≥ 70 (U/l)

Response of α -ETK activity to vitamin supplementation (α -ETK is the activity coefficient for ETK, calculated by dividing the enzyme activity in the presence of added co-factor by the activity in the absence of co-factor thus yielding a measure of deficiency)

Group (n)	Day 0			Day 2			Day 5		
	Mean	SD	Normals	Mean	SD	Normals	Mean	SD	Normals
Gp A (26) i.v.	1.143	0.070	16	1.154	0.074	14	1.093**	0.47	22
Gp B (24) oral	1.170	0.077	10	1.149	0.085	14	1.104**	0.058	18
Gp C (23) Placebo	1.140	0.065	14	1.139	0.058	11	1.090**	0.038	22
Totals (73)	-	-	40	-	-	39	-	-	62

The number of normals is the number of patients inside the normal range of ≤ 1.15

Authors' Conclusion:

- *'Irrespective of treatment regime, ETK activities rise and α -ETK values fall, but a substantial number of patients in all groups remain deficient.'*
- *'We have shown that a majority of chronic alcoholics are found to be thiamine-deficient as defined by low ETK activities, yet a lower proportion are deficient if defined by elevated α -ETK values.'*
- *'In the case of thiamine (and pyridoxine) the apparent degree of improvement depends on the specific parameter of assessment used. Nonetheless, a substantial number of patients remain deficient after 5 days despite supplementation with vitamins.'*

Limitations:

- The measures ETK and α -ETK may not be the most accurate measures of tissue thiamine levels.
- The doses of oral and parenteral thiamine given were not equal

Both groups were given i.v. thiamine at the start which may have affected the final results.

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