Prevention is Better than Cure

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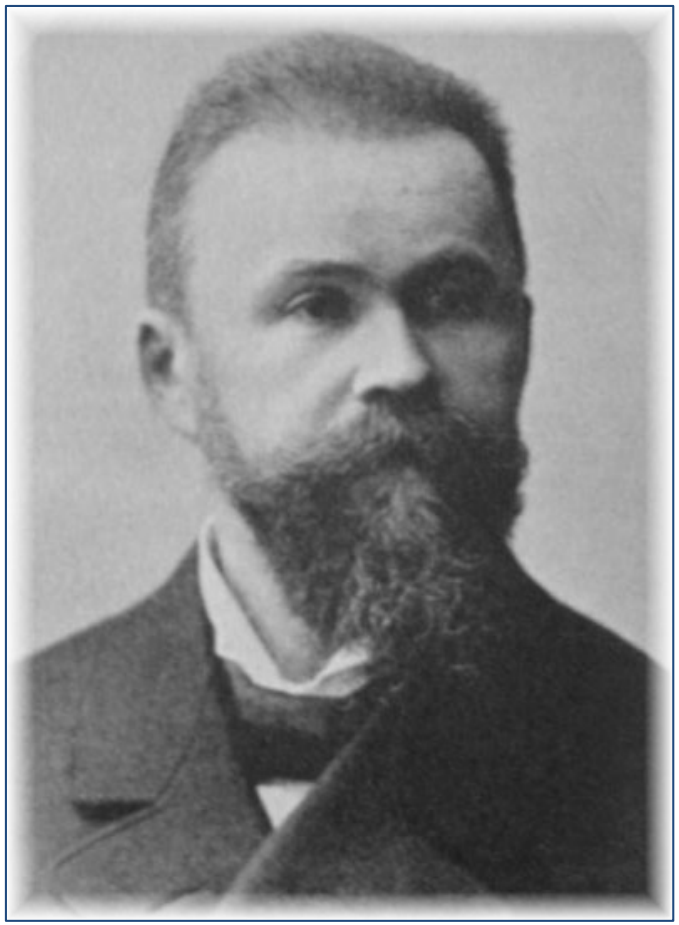
Korsakoff Symposium Meeting: Nijmegen
29 November 2019

Introduction

- 1845: Passing of County Asylum/Lunacy Act
- 1864: Opening of Glamorgan County Asylum
- 1874: Half of male patients in the Glamorgan County Asylum were there as a result of heavy drinking (Yellowlees)

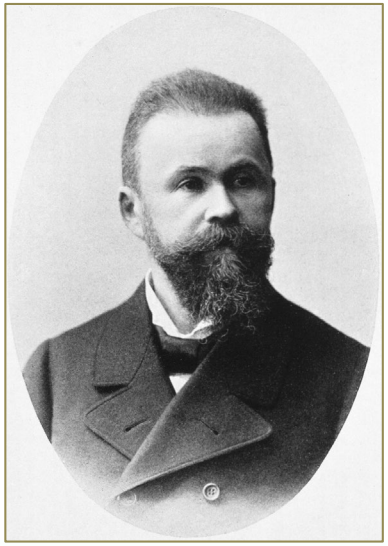


Carl Wernicke

1848-1905

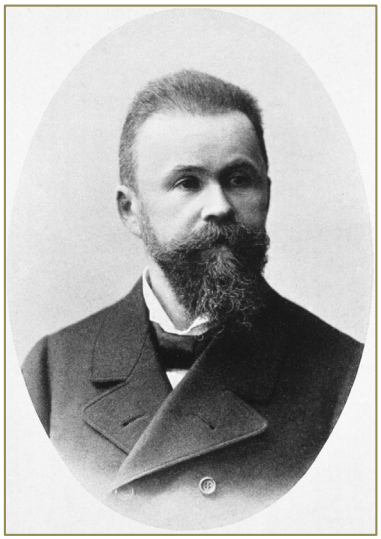
Carl Wernicke

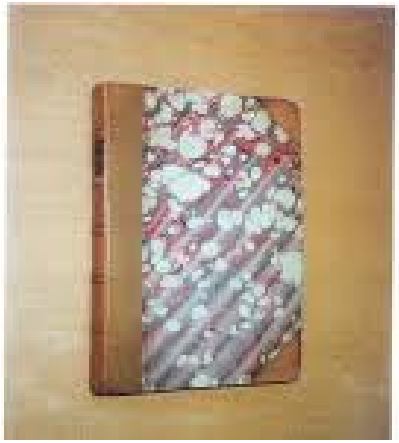
- 1881 paper on three patients, studied in life and at autopsy
- *Lehrbuch der Gehirnkrankheiten*
- Described a clinical syndrome
  - Clouding of consciousness
  - Varying ophthalmoplegias
  - Ataxia
- Haemorrhagic lesions in periventricular grey matter



Wernicke's Encephalopathy

- Nystagmus, ophthalmoplegia, ataxia, global confusion
  - Acute onset
  - Occurring together or in various combinations
- Thiamine (B1) deficiency
- Can be prevented and treated successfully
- Recurrent sub-clinical episodes may lead to a more chronic form
- Left untreated can progress to Korsakoff's





Sergei Korsakoff 1854-1900

Sergei Korsakoff

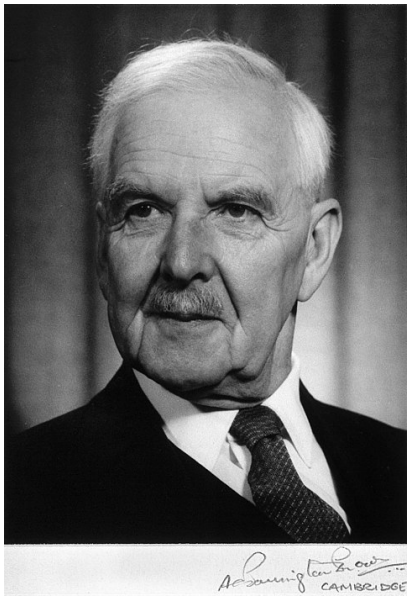
First comprehensive description of the unique amnestic syndrome (1887)

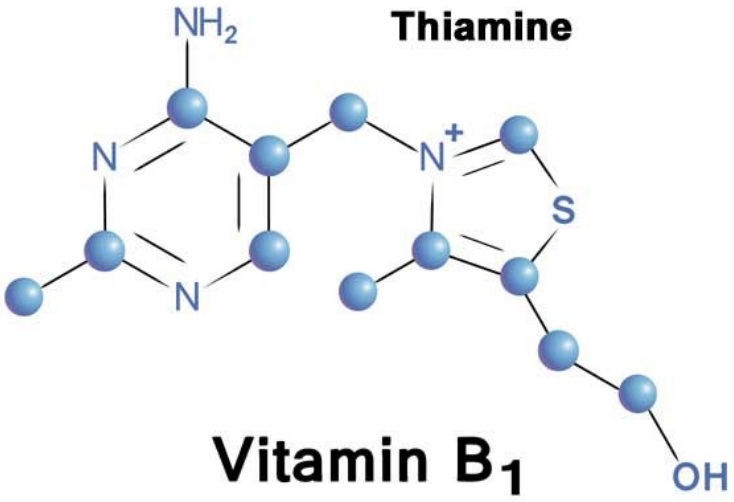
Syndrome elaborated in a series of articles between 1887 and 1891

His third article (1889) was translated into English by Victor and Yakovlev (1955)

Thiamine

- 1929: Sir Rudolph Peters, Oxford. Thiamine deficient pigeons - “biochemical lesion”

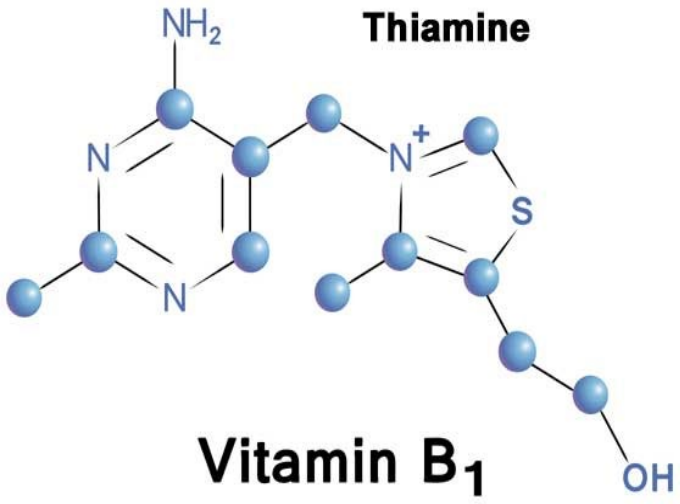




Thiamine depletion as cause of WE

- Bender and Schilder, 1933
- Jolliffe et al, 1941

- Victor, 1966 – recommended thiamine replacement in WE



Hugh Edward de Wardener: 1915-2013

- Prisoner of war in Burma (WW2)
- Recognised WE in malnourished soldiers
- Realised the dietary causation
- Treated soldiers with Marmite
- Seminal Lancet paper 1947

Victor, Adams and Collins, 1971, 1989

- The Wernicke-Korsakoff Syndrome and Related Neurologic Disorders Due to Alcoholism and Malnutrition. Philadelphia: FA Davis Co, 1989

- Clinico-pathological correlations – WKS
- Definition of KS
  - …an abnormal mental state in which memory and learning are affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient…

What is the true prevalence of WE?

- Reported prevalence in autopsy series: 0.4-2.8% (average 1.3%)
- WE can occur in a number of conditions
- More prevalent in alcoholics
  - 12.5% (Harper, 2006; Harper et al, 1988; 2003)
- Frequently undiagnosed during life
- Autopsy studies are likely to be biased to more severe cases
  - Incidence is probably underestimated

Prevalence of Wernicke's Encephalopathy: Autopsy series

Author	Series	Country	Incidence %
Cravioto et al, 1961	1957-1960 N = 1600 brains (28 cases)	Bellevue Hospital, New York, USA	1.7%
Victor and Laureno, 1978	1963-1976 N = 3548 consecutive autopsies	Metropolitan Hospital, Cleveland, USA	2.2%
Torvik et al, 1982	1975-1979	Oslo, Norway	0.8%
Harper et al, 1983	1973-1981 N = 4677 brains (131 cases)	Royal Perth Hospital, Western Australia	2.8% (4.7% in brains from the Coroner's Dept)
Hauw et al, 1988	1952-1983 N = 8200	France	1.4%
Lindboe and Loberg, 1989	1983-1987 N = 6964	Norway	0.7%

Studies with autopsy confirmation of WE

- Wernicke, 1881
- Korsakoff, 1889
- Campbell and Biggart, 1939 (N=12)
- Riggs and Boles, 1944 (N=42)
- De Wardener and Lennox, 1947 (N=52)
- Barrie, 1947 (N=3)
- Cravioto et al, 1961 (N=28)
- Grunnet, 1969 (N=24)
- Victor et al, 1989 (N=245)
- Wallis et al, 1978 (N=4)
- Torvik et al, 1982 (N=70)
  - Mainly stupor and coma
- Harper et al, 1986 (N=97)
- Lindboe and Loberg, 1989 (N=52)
  - Mainly disorientation, depressed consciousness, eye signs (in 3 cases only)
  - Thiamine given too late
- Fattal-Valevski et al, 2005 (N=9)
  - Infants fed thiamine deficient soy formula
- Harper, 2006 (N=44)

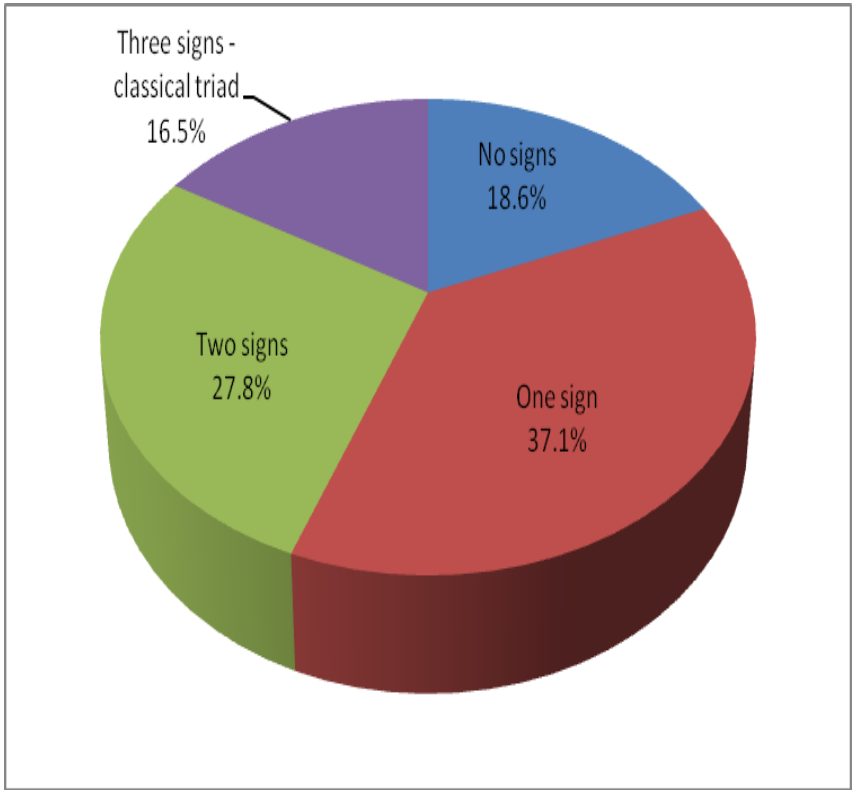
Characteristics and neuro-pathological findings in alcoholic WKS

	Malamud & Skillicorn	Victor et al.
N	70	245
Gender (M:F)	52:18	154:91
Mean age at onset (y)	58	51 (est.)
History of alcoholism N (%)	63 (90 %)	243 (99 %)
Neuropathology (%)		
Mammillary bodies	96	100
Dorsomedial thalamus	53	88
Pulvinar	4	85
Brainstem nuclei	23	55
Cerebellum	34	56

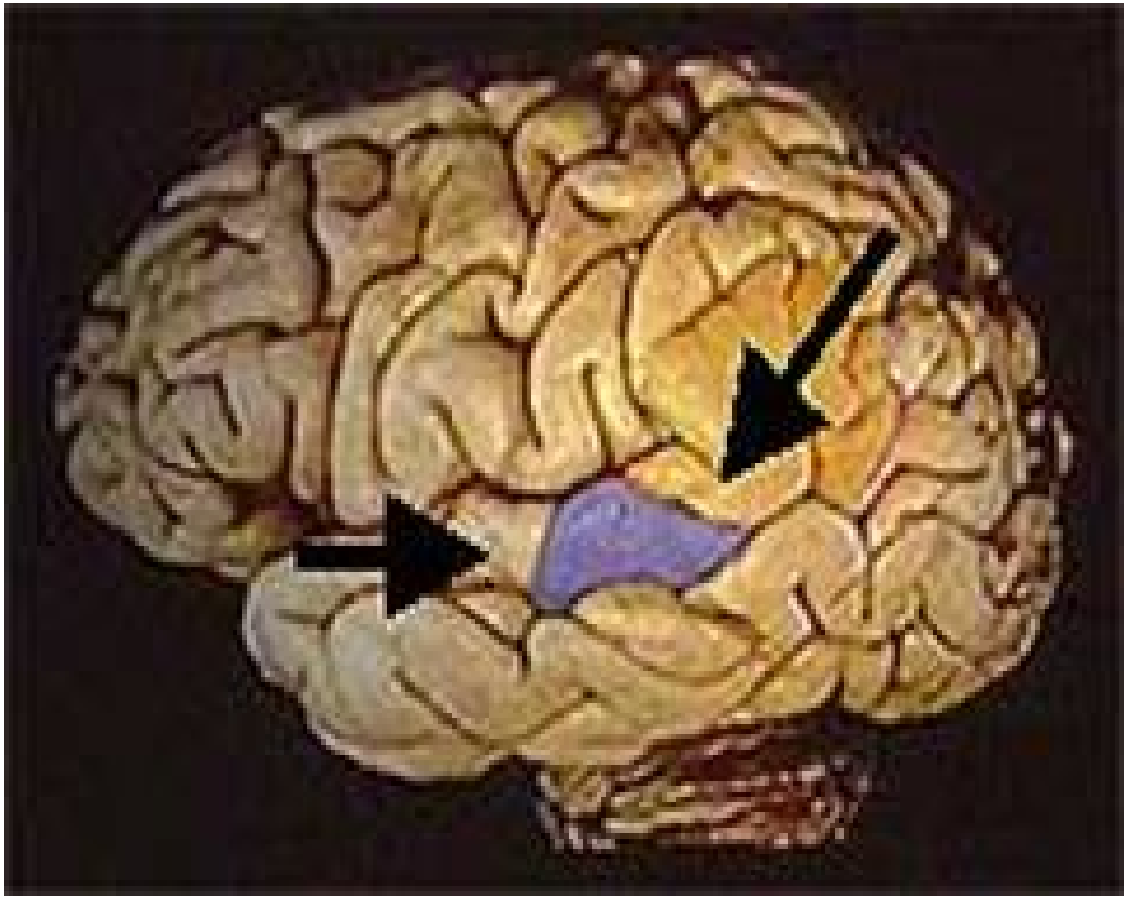
Kril and Harper, 2012

Wernicke's Encephalopathy

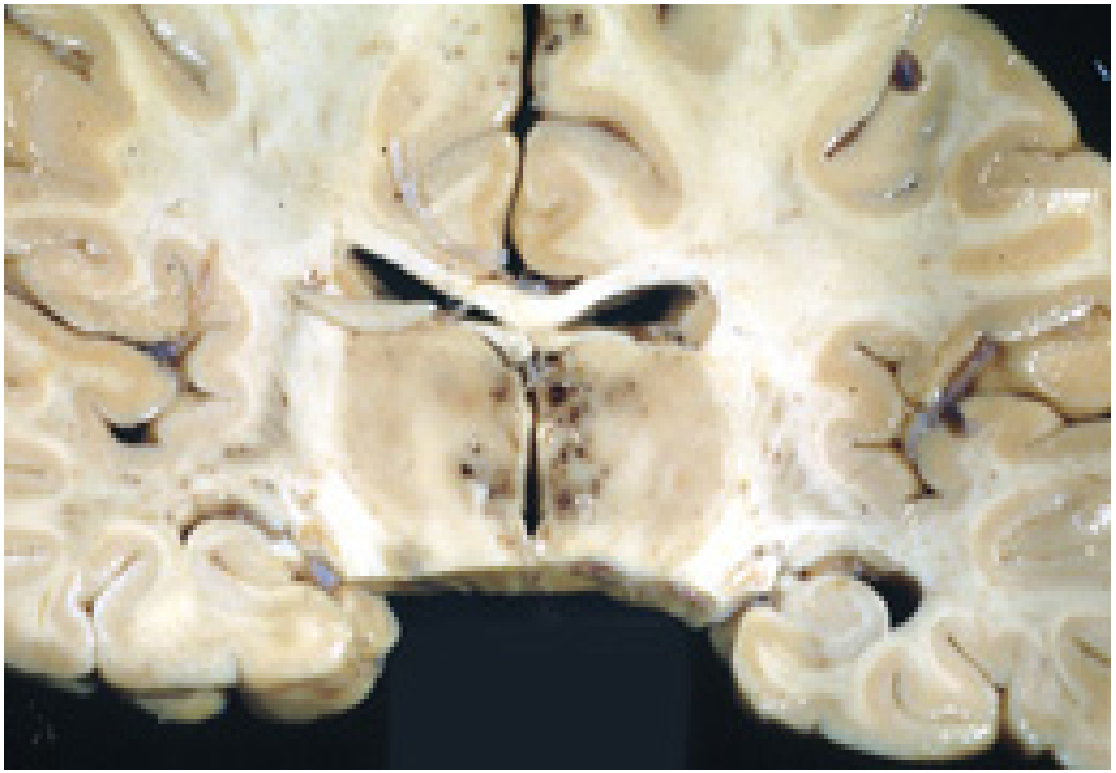
- Harper et al (1986)
  - Diagnosis of WE not made during life in 80% of cases (Harper et al, 1986)
  - 16% of cases diagnosed at autopsy had the classic triad of clinical signs (confusion, ataxia, eye signs)
- Brains often appear normal macroscopically
- Unless appropriate blocks are examined microscopically, 30% of cases will be missed



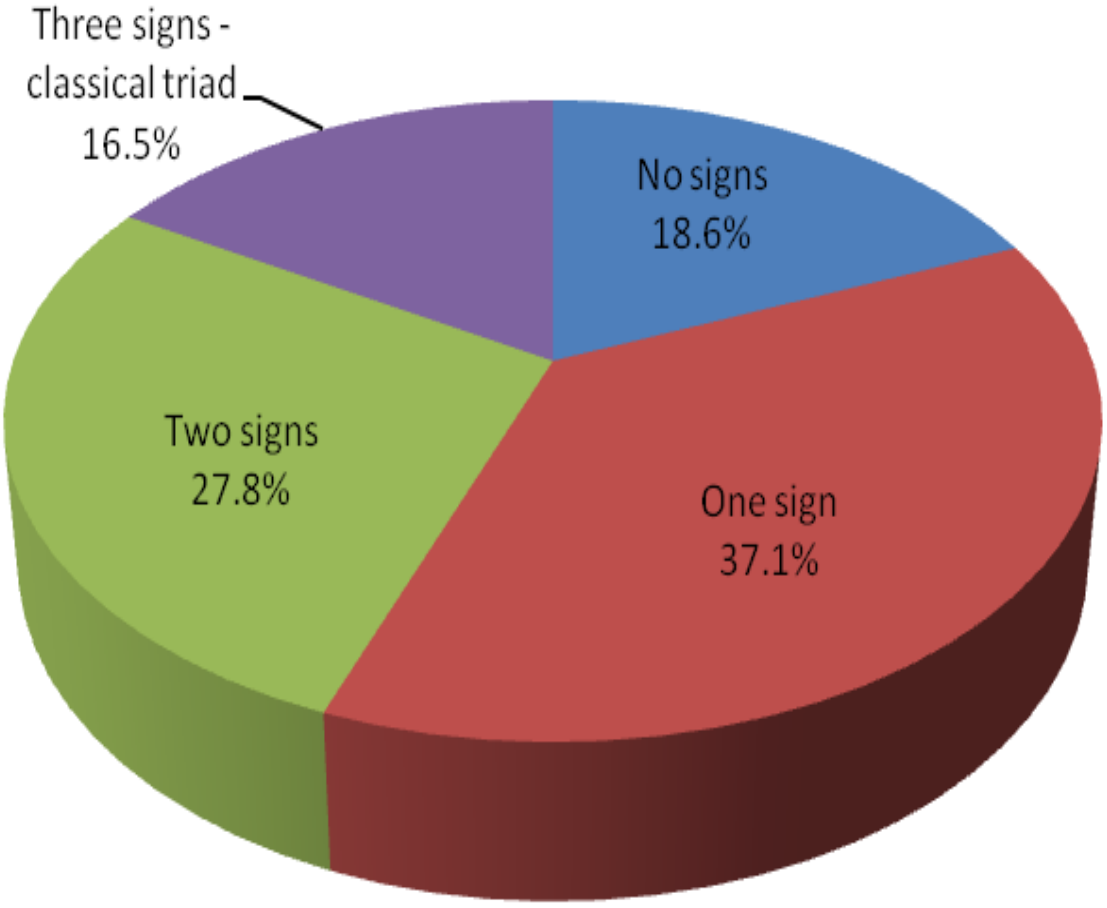
Wernicke Korsakoff Syndrome



Wernicke Korsakoff Syndrome



Incidence of clinical signs of Wernicke-Korsakoff Syndrome [Adapted from Harper *et al.* 1986]



97 cases of WE (94 with alcohol misuse)
94 diagnosed at PM

Table 4 Clinical features of patients with an autopsy proved diagnosis of Wernicke encephalopathy

Authors [reference]	Evidence class	Total no. of patients	Dietary deficiencies	Nausea and vomiting	Any eye sign	Cerebellar signs	Seizures	Amnesia, mild memory impairment	Altered mental state	Triad
Cravioto [38]	IV	28	14		9	5			26	4
Grunnet [61]	IV	24	1		9	3	4	4	17	0
Torvik [41]	IV	19			4	0			18	0
Harper [62]	IV	97			28	36		29	41	16
Lindboe [46]	IV	18			3	0			11	0
Naidoo [49]	IV	17	1	8	0	2			9	0
Vege [51]	IV	4	2	1	0	0	1	2	3	0
Ogershok [59]	IV	4	3		4	1			4	1
Bleggi-Torres [63]	IV	8			3	0			6	0
Harper [56]	IV	18			0	3	3	6		0
Bertrand [58]	IV	19			2	15		19	1	0
Total *N* (%)		256	21 (8.2)	9 (3.5)	62 (24.2)	65 (25.4)	8 (3.1)	60 (23.4)	136 (53.1)	21 (8.2)

Classic triad reported for only 8% of patients with clinical details

Galvin et al, 2010

WERNICKE'S ENCEPHALOPATHY: 'PLUS CA CHANGE, PLUS C'EST LA MEME CHOSE'

ALLAN D. THOMSON[1,4], CHRISTOPHER C. H. COOK[2], IRENE GUERRINI[1], DONNA SHEEDY[3], CLIVE HARPER[3] and E. JANE MARSHALL[4]*

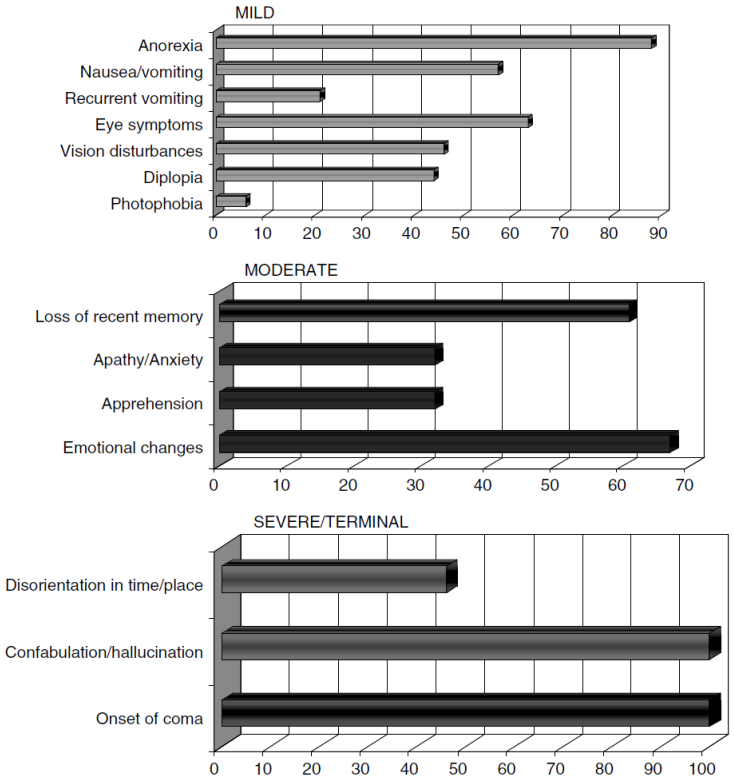
Alcohol & Alcoholism Vol. 43, No. 2, pp. 180–186, 2008

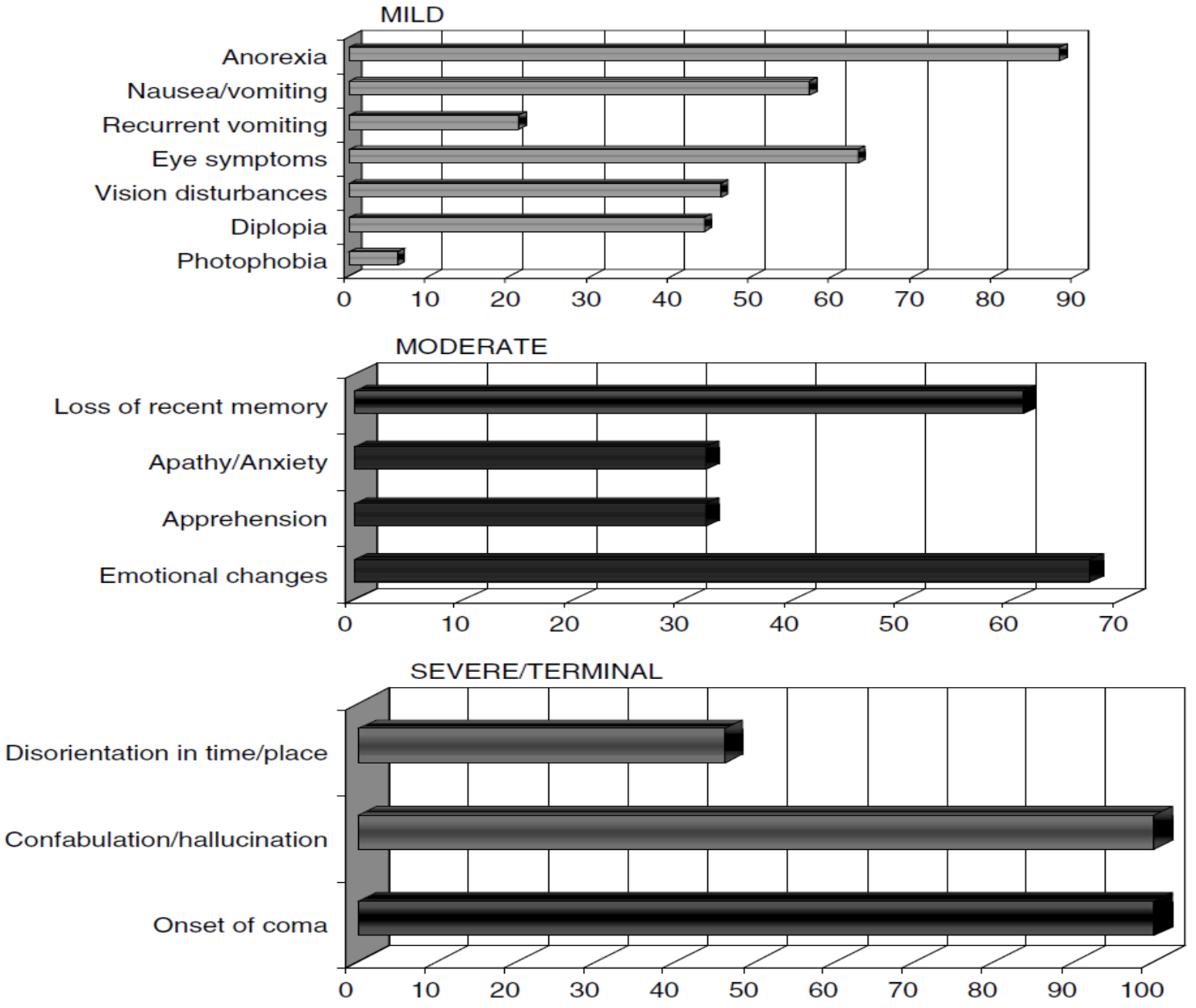
Table 1. Recorded clinical findings in patients whose diagnosis of WKS has been confirmed at post-mortem The percentages refer to the frequency with which the signs/symptoms appear in each group have been included where available

	Wernicke			Korsakoff	Campbell and Biggart.	Riggs and Boles.	De Wardener and Lennox	Barrie	Craviato *et al.*	Grunnet.	Victor *et al.*	Wallis *et al.*	Torvik *et al.*	Harper *et al.*	Lindboe and Loberg	Fattal	Harper*
	1881			1889	1939	1944	1947	1947	1961	1969	1989	1978	1982	1986	1989	2005	2006
PTS. No.	F 20	M 36	M 33		12	42	52	3	28	24	245	4	70	97	52	9	44
Loss of appetite			Y				Y (88%)				Y						
Weight loss	Y							Y			Y						Y (25%)
Nausea & Vomiting	Y		Y	Y			Y (78%)				Y					Y (89%)	Y (7%)
Fatigue & weakness		Y		Y							Y	Y					
Apathy & lethargy	Y		Y	Y	Y		Y (32%)		Y		Y		Y			Y (78%)	
Fear	Y	Y															
Apprehension					Y	Y	Y (32%)										
Emotional Instability						Y	Y (67%)										
Confusion	Y			Y	Y	Y	Y (100%)	Y	Y	Y (50%)		Y	Y				Y (34%)
Impaired memory				Y			Y (61%)	Y	Y		Y		Y	Y (30%)			Y (40%)
Giddiness	Y		Y				Y (21%)										
Insomnia		Y			Y		Y (38%)										
Anxiety/Depression	Y			Y		Y	Y				Y						
Difficulty in concentration				Y			Y				Y						
Disorientation	Y		Y				Y (46%)		Y	Y (50%)	Y	Y		Y (42%)	Y		Y (5%)
Confabulation				Y	Y		Y (100%)		Y	Y (12.5%)	Y						
Hallucinations					Y		Y			Y (8%)	Y						
Stupor		Y	Y								Y		Y				
Staggering/Ataxia		Y		Y		Y	Y		Y	Y (12.5%)	Y	Y		Y (37%)			Y (25%)
Ophthalmoplegia Diplopia/Ocular Abnormalities	Y	Y			Y	Y	Y (98%)	Y	Y	Y (16.7%)	Y	Y		Y (4%)*	Y		Y (3%)
Nystagmus					Y	Y	Y (100%)		Y	Y (8%)	Y	Y	Y	Y (10%)	Y	Y (22%)	
Delirious		Y	Y	Y	Y	Y	Y				Y						
Motor Restlessness		Y	Y	Y									Y				
Peripheral neuropathy			Y	Y			Y (52%)	Y	Y	Y (12.5%)	Y	Y					Y (25%)
Coma					Y		Y (100%)	Y			Y	Y	Y		Y		
Fits						Y	Y (2%)			Y (2%)	Y						Y (7%)

Clinical Diagnosis of non-alcoholic WE

- De Wardener and Lennox (1947) graded the severity of WE in their sample
- Mild, moderate and severe phases of WE had distinctive signs and symptoms
- The symptoms were reversed in approx the same chronological order following treatment





De Wardener and Lennox, 1947

Caine Criteria

Caine et al 1997

Clinical diagnosis of WE requires two of the following four signs:
(i) Dietary deficiencies
(ii) Eye signs
(iii) Cerebellar dysfunction
(iv) Either mild memory impairment or an altered mental state

Caine et al (1997)	
28 autopsy proven patients with WE well evaluated during life	Tested criteria on records of the 106 autopsied patients
Signs and symptoms developed into 8 clinical domains:	Sensitivity ranged from: 20% (seizures) - 75% (cerebellar signs)
•Dietary deficiencies •Eye signs •Cerebellar signs •Seizures •Frontal lobe dysfunction •Amnesia •Mild memory impairment •Altered mental state	Sensitivity of classic triad: 23% Sensitivity rose to 85% if patient had at least 2 of following 4 features: • Dietary deficiencies • Eye signs • Cerebellar signs • Mild memory impairment or an altered mental state

Table 3. Incidence of clinical signs in WKS grouped according to Caine *et al*. (1997). Information on dietary deficiency was not complete

Author	Cases (no.)	Eye signs (%)	Ataxia (%)	Mental changes (%)
Harper (unpublished data)	44	3	25	79
Fattal-Valevski *et al*. (2005)	9	33	22	56
Lindboe and Loberg (1989)	52	21	NA	6
Harper *et al*. (1986)	97	29	37	76
Victor *et al*., (1989)	163/232	100	100–81	99
Wallis *et al*. (1978)	4	0	NA	100
Groen and Hoff (1977)	50	80	46	88
Grunnet (1969)	24	25	13	75
De Wardener and Lennox (1947)	52	100	NA	100
Cravioto *et al*. (1961)	28	32	18	93
Barrie (1947)	3	67	0	100
Riggs and Boles (1944)	42	24	10	86
Campbell and Biggart (1939)	12	42	0	92

Diagnosis of WE

- Consistent pattern of signs and symptoms
- The pattern is broadly similar for “nutritional” thiamine deficiency and for thiamine deficiency plus alcohol misuse
  - but there are differences see next slide
- The diagnosis of WE not made prior to death in 80% of cases
- Difficult to establish a true prevalence of WE without accurate autopsy data
- Fewer autopsies: ? diagnostic role for neuro-imaging
- WE still a clinical diagnosis

Features of alcoholic and non-alcoholic WE

Galvin et al, 2010

Alcoholic Wernicke's Encephalopathy	Non-alcoholic Wernicke's Encephalopathy
	Dietary deficiency
	Vomiting
Eye signs	
Cerebellar signs	
Classic triad	

Alcoholic Wernicke's may present more frequently as a sub-clinical syndrome	Non-alcoholic Wernicke's more likely to present as an acute syndrome (?)
Multiple episodes of thiamine deficiency	
Magnesium deficiency may contribute to the poor recovery in alcoholics	

Factors predisposing to thiamine deficiency

- Weight loss in past year
- Reduced Body Mass Index
- General clinical impression of nutritional status
- High carbohydrate intake
- Recurrent episodes of vomiting in the past month
- Co-occurrence of other nutritionally related conditions (polyneuropathy, amblyopia, pellagra, anaemia)

Factors predisposing to neurotoxicity

- Genetic predisposition to alcohol dependence and neurotoxic effects of alcohol
- Quantity/frequency of alcohol use
- Severity of dependence
- Frequent episodes of acute intoxication
- Withdrawal syndromes
- Concurrent drug use, particularly cocaine
- Alcohol-related liver damage

Thomson et al, 2009

Clinical evaluation of patients at risk of thiamine deficiency

Early signs and symptoms of thiamine deficiency

- Loss of appetite
- Nausea/vomiting
- Fatigue, weakness, apathy
- Giddiness, diplopia
- Insomnia, anxiety, difficulty in concentration
- Memory loss

Later signs and symptoms

- Classic triad: oculomotor abnormalities, cerebellar dysfunction (ataxia) and confusion
- Quiet global confusion with disorientation in time/place
- Confabulation/hallucination
- Onset of coma

Thomson et al, 2009; 2012

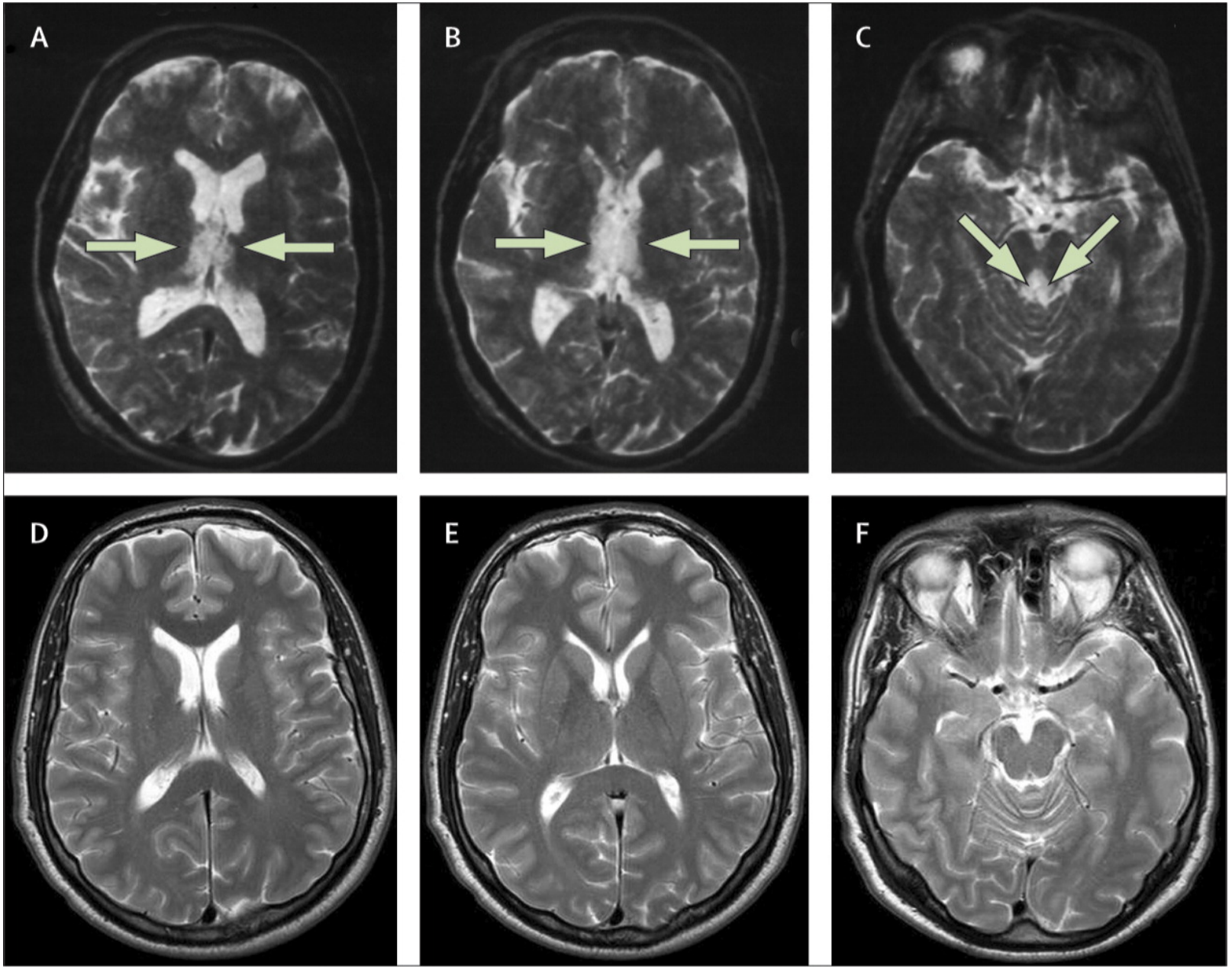
Can laboratory testing help?

- Thiamine blood levels
  - Do not reflect brain levels of thiamine diphosphate
  - Do not predict the development of WE
- No defined circulating blood thiamine level at which WE develops in all patients
- May indicate those at immediate risk
- Direct measurement of thiamine by HPLC (Galvin et al, 2010)
  - Assay commercially available
  - 2ml EDTA blood should be taken before administration of thiamine
  - Normal range: 60-220nM; Lowest detectable range: 3-35nM
- Normal thiamine levels do not necessarily exclude diagnosis of WE (thiamine transporter gene mutations)

Can neuro-imaging help?

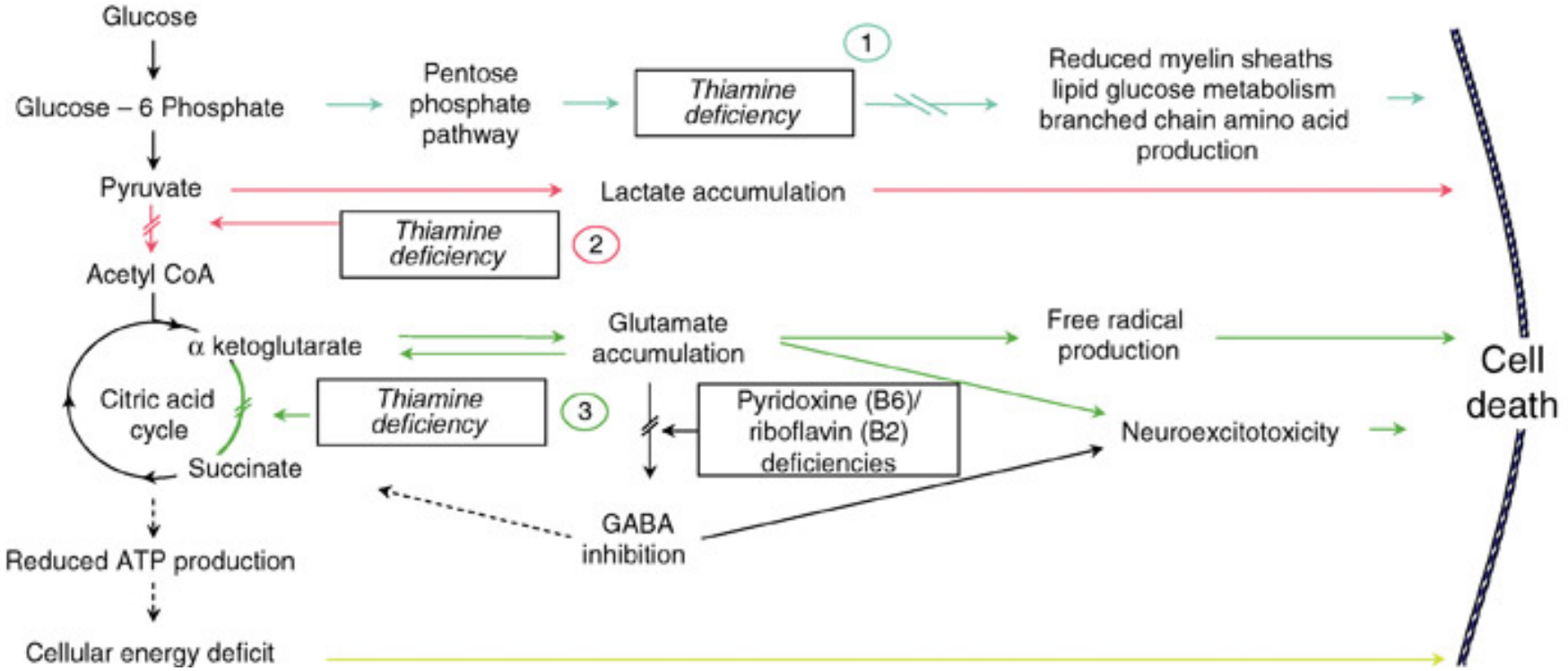
- MRI scans reveal lesions in nearly ⅔ of subjects with clinically verified WE
- Lesions are typically symmetrical and seen in
  - Thalami; mammillary bodies; tectal plate; periaqueductal area
- Atypical lesions (more frequent in non-alcoholics) seen in
  - Cerebellum, vermis, caudate nuclei, red nuclei, dentate nuclei, splenium, cerebral cortex
- Reversible cytotoxic oedema considered the most distinctive lesion

Galvin et al, 2010


A
B
C
D
E
F

Thiamine Deficiency and the "Alcoholic" Brain

- Alcohol dependence:
  - Neuro-adaptation in GABA and glutamate systems
  - Frequent episodes of intoxication and withdrawal lead to glutamate-induced excitability and neuronal damage
  - Requirement for thiamine increased during withdrawal
  - Thiamine deficiency causes excessive glutamate release
- Case reports of WE indicate it often occurs during a period of sudden unexpected and untreated alcohol withdrawal


Glucose
Glucose – 6 Phosphate
Pentose phosphate pathway
1
Thiamine deficiency
Reduced myelin sheaths lipid glucose metabolism branched chain amino acid production
Pyruvate
Lactate accumulation
Thiamine deficiency
2
Acetyl CoA
α ketoglutarate
Glutamate accumulation
Free radical production
Cell death
Citric acid cycle
Thiamine deficiency
3
Pyridoxine (B6)/ riboflavin (B2) deficiencies
Neuroexcitotoxicity
Succinate
GABA inhibition
Reduced ATP production
Cellular energy deficit

Animal Studies of Thiamine Deficiency

- Experimental animal models of TD
  - Drug-induced/diet-induced
- Dietary thiamine deficiency in rhesus monkeys
  - One episode: lesions in inferior colliculus and medial vestibular nuclei
  - Lengthy episodes: lesions in basal ganglia
  - No lesions seen in mammillary bodies and dorso-medial nucleus of thalamus, though monkeys showed evidence of memory deficits similar to those seen in WKS patients (Witt and Goldman-Rakic, 1983)

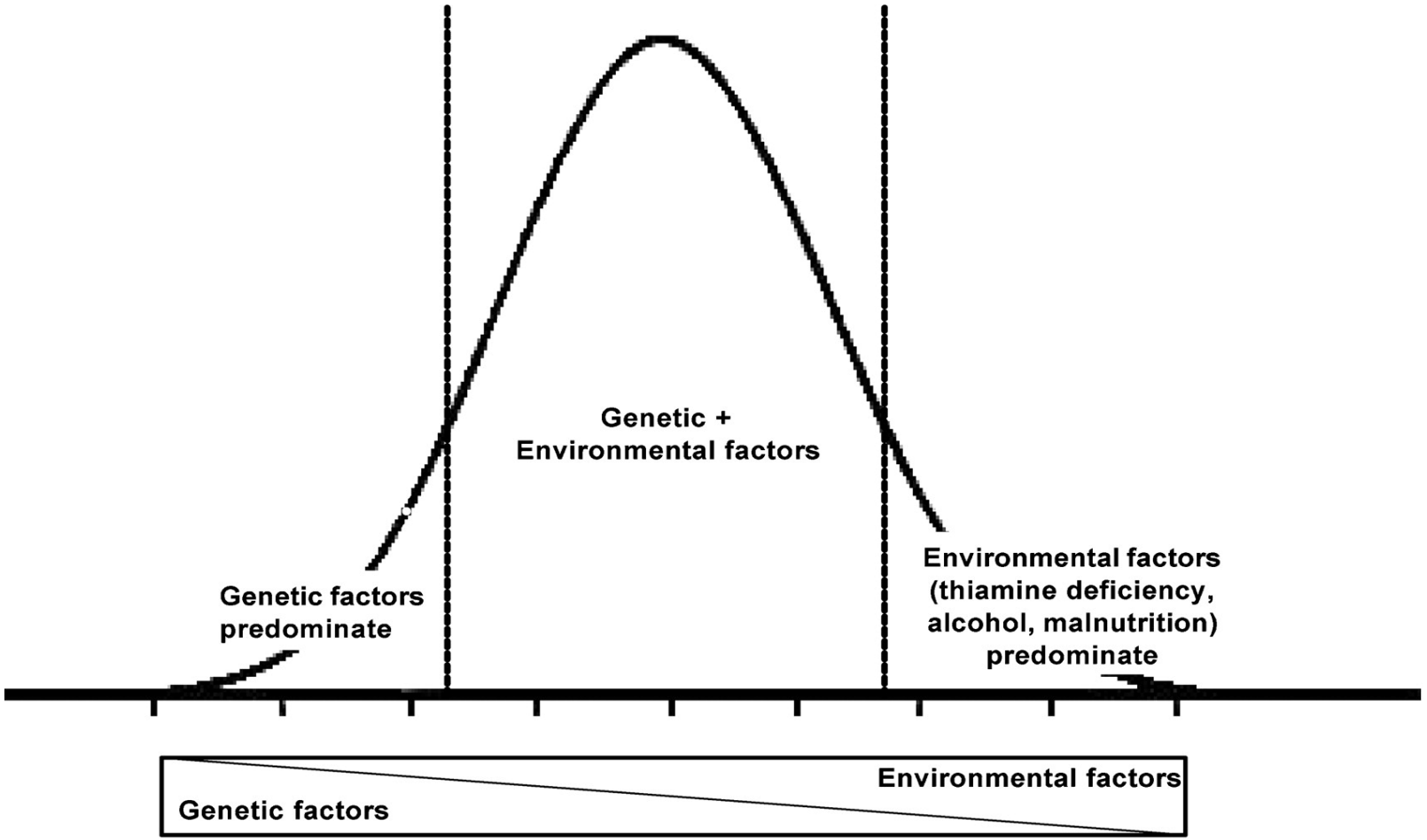
Pathophysiology of Wernicke's Encephalopathy

- Genetic predisposition
- Inadequate intake of thiamine (B1)
- Impaired absorption of thiamine: active transport; liver damage; reduced thiamine phosphorylation
- Thiamine transport problems: GIT, blood–brain barrier, neurones
- Increased demand for thiamine: alcohol withdrawal; DTs; NMDA receptors
- Alcohol intake: neurotoxicity; damage to apoenzymes; increased metabolic demands
- Organ damage: liver damage, reduced thiamine phosphorylation
- Other nutritional deficiencies: B12, folate
- Predisposing diseases
- Inadequate treatment

Thomson et al 2009; 2012

Genetic Predisposition

- 80% of brain thiamine is in form of thiamine diphosphate (TDP)
  - TDP is a co-factor for three thiamine dependent enzymes:
    - α ketoglutarate dehydrogenase; transketolase; pyruvate dehydrogenase
  - Reductions of thiamine-dependent enzymes in autopsied cerebellar vermis from alcoholic patients with WKS (Butterworth et al, 1993)



(Guerrini & Thomson, 2005)

Thiamine Transporters

- Thiamine-transporter 1 and Transporter 2 (products of SCL19A2 and SCL19A3 genes)
- Well expressed in intestine, kidneys and brain (Guerrini et al, 2005)
- SCL19A2 gene encodes the human thiamine transporter protein (497 amino acids)
  - Mapped to 1q23-q23.3
  - First identified in group of Iranian families affected by a thiamine-responsive megaloblastic anaemia syndrome (TRMA): autosomal recessive

Thiamine Transporters

- SCL19A3 a second thiamine transporter
- Recently mapped to chromosome 2q37
- Thiamine-transporter-2 deficiency
  - Recessive inherited defect
  - Mutations in the SCL19A3 gene
  - Causes acute and recurrent episodes of encephalopathy, seizures and brain injury (Kono et al, 2009)
  - Responds well to early administration of thiamine and biotin (Kono et al, 2009: Ortigoza-Escobar et al, 2014)
  - Timely and effective treatment depends on clinical suspicion

Reduced Availability of Thiamine

- Inadequate intake
  - Total body stores only 30g and deplete in a few weeks (daily requirement of 1-2g)
- Impaired absorption
  - Alcohol/liver damage
- Thiamine transporter problems
- Other nutritional deficiencies
  - Folate, B6, B12
- Effects of low circulation thiamine levels
  - Reduction in activity of thiamine-dependent enzymes, alterations in mitochondrial activity, impaired oxidative metabolism, decrease energy, selective neuronal death

Recommended Dietary Allowances (RDAs) for Thiamine

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months*	0.2 mg	0.2 mg		
7–12 months*	0.3 mg	0.3 mg		
1–3 years	0.5 mg	0.5 mg		
4–8 years	0.6 mg	0.6 mg		
9–13 years	0.9 mg	0.9 mg		
14–18 years	1.2 mg	1.0 mg	1.4 mg	1.4 mg
19-50 years	1.2 mg	1.1 mg	1.4 mg	1.4 mg
51+ years	1.2 mg	1.1 mg		

Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press; 1998.

Disorders co-existing with alcohol use disorders may increase the risk of developing WE

- Diabetic ketoacidosis
- Chronic renal failure
- Severe obesity
- Ulcerative colitis
- Pernicious anaemia
- Anorexia nervosa
- Patients with Alzheimer's disease
- Neglect in old age, especially if living alone
- Chronic schizophrenia
- Widespread tuberculosis
- AIDS
- Teenage pregnancy with poor nutrition/drug misuse while mother still growing
- Patients with protracted vomiting, including during pregnancy
- Sepsis

Table 3 List of cases of Wernicke encephalopathy reported in non alcoholic subjects[a]

Clinical condition	No.	%
Cancer	113	18.1
Gastrointestinal surgery	105	16.8
Hyperemesis gravidarum	76	12.2
Starvation/Fasting	64	10.2
Gastrointestinal tract diseases	48	7.7
AIDS	31	5.0
Malnutrition	26	4.2
Dialysis and renal diseases	24	3.8
Parenteral nutrition	24	3.8
Vomiting	15	2.4
Psychiatric diseases	15	2.4
Stem cell/marrow transplantation	14	2.2
Infections	9	1.4
Intoxication	9	1.4
Thyroid diseases	8	1.3
Unbalanced diet	6	1.0
Iatrogenic	5	0.8
Hypoxic encephalopathy	2	0.3
Others	12	1.9
Unknown etiology	19	3.0
Total	625	100.0

[a]Search performed in Medline, Embase, LILACS from data-base inception through May 31, 2009.

Risk for WE after bariatric surgery is long-lasting

Most cases are seen within 6 months

Increasing numbers of case reports/series being published

Thiamine status should be followed up for at least 6 months post surgery

Galvin et al, 2010

Treatment of Wernicke's Encephalopathy

- Treatment of suspected WE must be prompt
  - Delayed treatment increases likelihood of death, KS
- In patients with alcohol misuse rapid correction requires a high plasma concentration to cross the blood-brain barrier
- Guidelines stipulate at least 3 days of treatment with IV thiamine BUT thiamine should be given for as long as improvement is observed (Thomson et la, 2012)

From: Osiezagha et al 2013

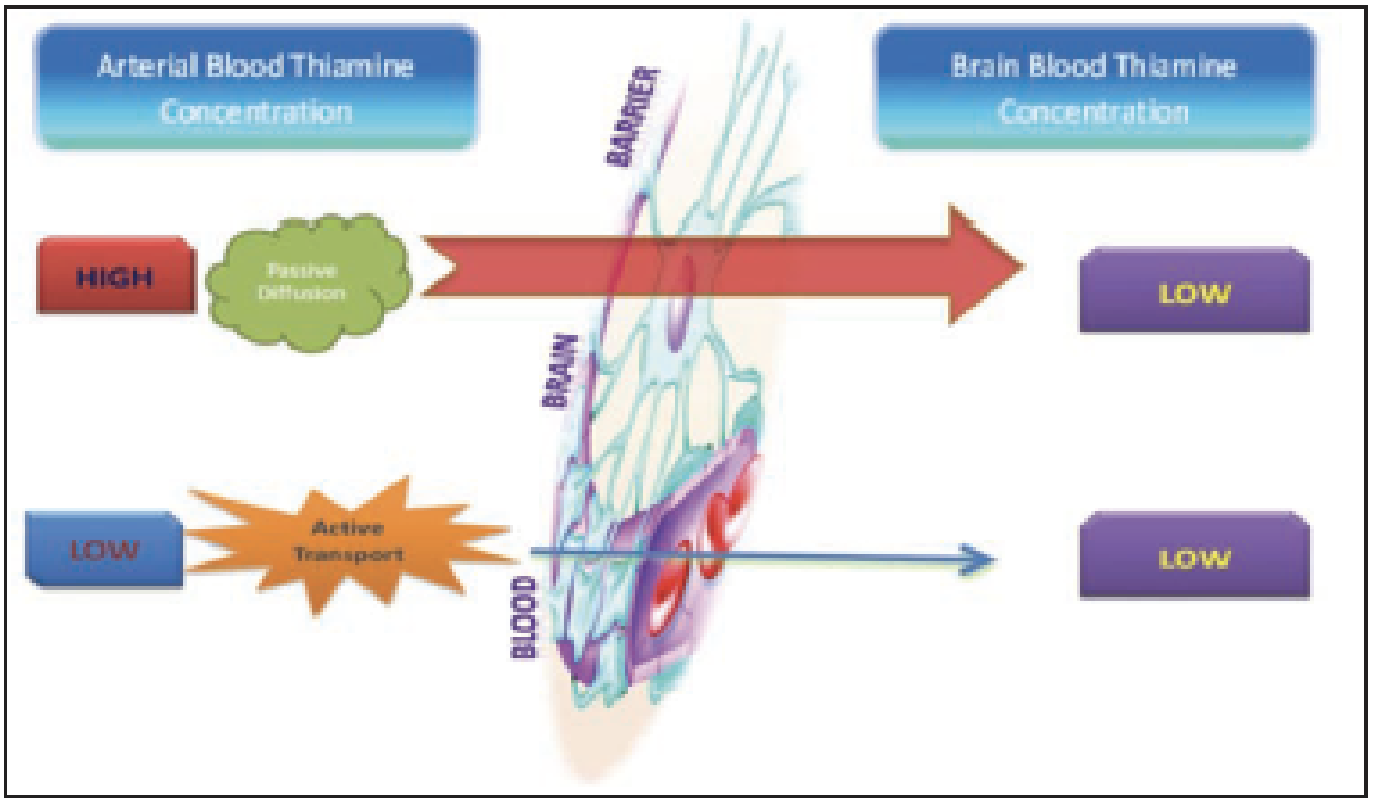


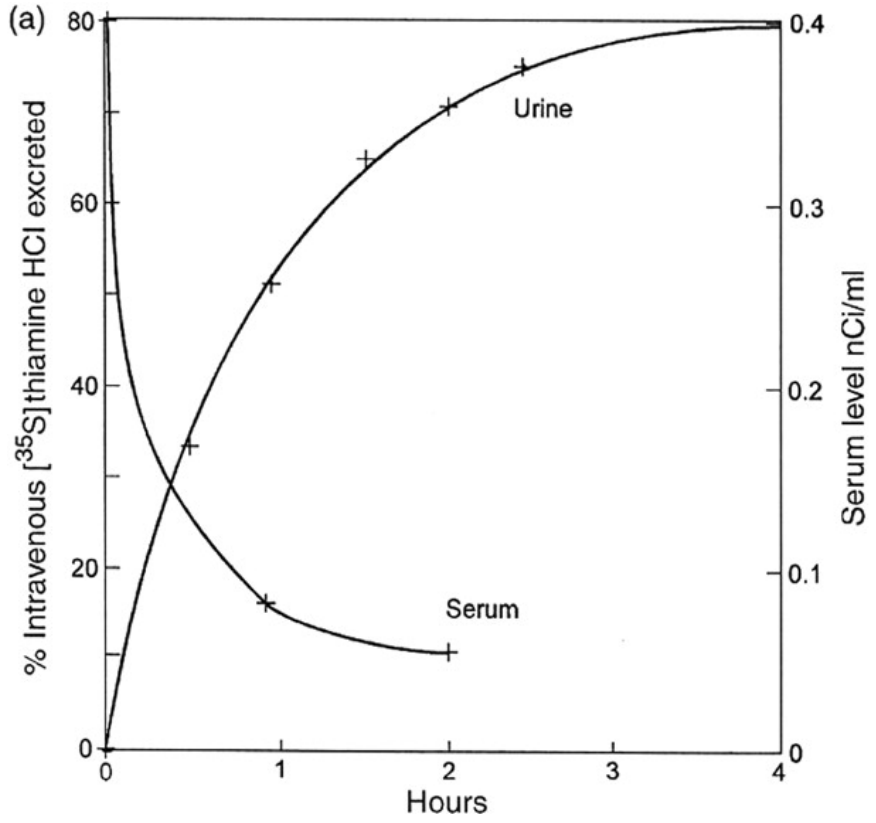
FIGURE 1. Transportation of thiamine through the blood brain barrier

Table 3 The immediate treatment of Wernicke's Encephalopathy

- Thiamine 500 mg IV three times daily for 2-to-3 days and 250 mg IV daily for the next 3-to-5 days given as an infusion over 30 min, diluted in 50–100 mL of normal saline
- Thiamine 100 mg orally three times daily for the rest of the hospital stay and during outpatient treatment. Absorption will be <4.5 mg daily
- Multivitamins IV
- Replace magnesium: average deficit 2 mEq/kg
  - Replace as outlined by Flink 1969: check renal impairment
- Replace fluid and electrolyte losses: monitor electrolytes, blood pressure and renal function

IV=intravenously

Thomson et al, 2012


(a)
% Intravenous [35S]thiamine HCl excreted
Serum level nCi/ml
Urine
Serum
Hours
0
20
40
60
80
0
0.1
0.2
0.3
0.4
0
1
2
3
4

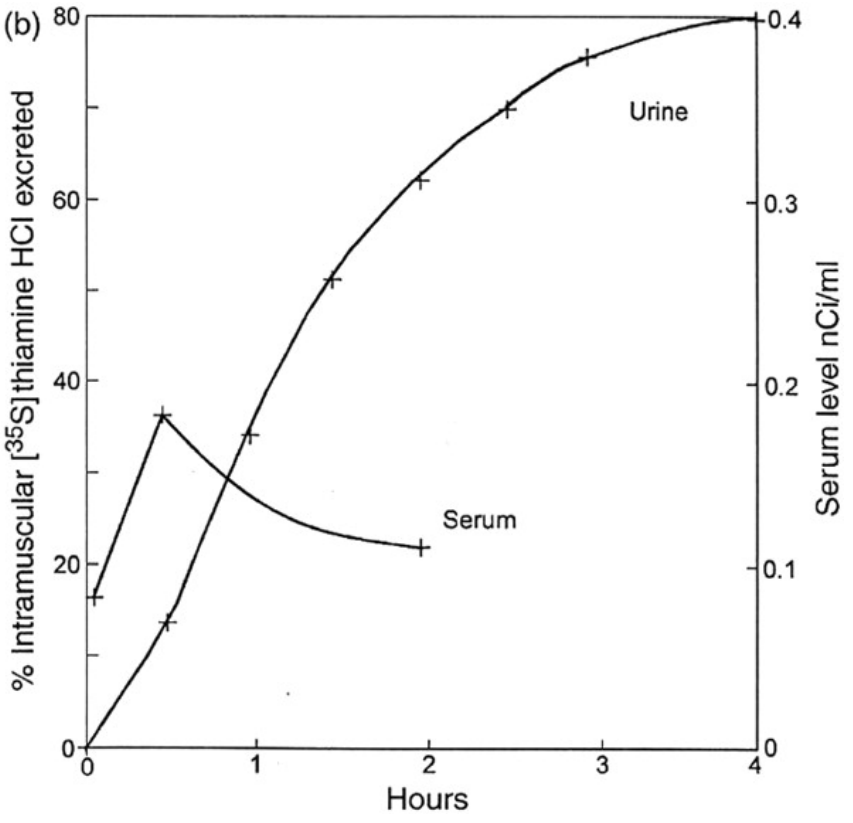

(b)
% Intramuscular [35S]thiamine HCl excreted
Serum level nCi/ml
Urine
Serum
Hours
0
20
40
60
80
0
0.1
0.2
0.3
0.4
0
1
2
3
4

Table 2. Audit findings relating to treatment and dose of parenteral thiamine

Author (year)	Study	Patients eligible for IV thiamine but not prescribed (%)	Prescribed incorrect dose (%)	Incorrect duration (%)
Collins (2005)	Audit of prescribing of IV Pabrinex in medical wards: $n = 53$ medical admissions No signs of WE: 11 Signs of WE: 26 At risk of WE: 16	—	Signs of WE: 13 (50%) At risk of WE: 16 (100%) Overall: 69%	57% of eligible patients
Johnston (2007)	$n = 52$ medical admissions with alcohol-related conditions 18 of 52 patients prescribed IV Pabrinex	61% (11/18)[a] 11 of the 18 prescribed Pabrinex did not receive it	—	—
Day *et al.* (2010)	Pharmacy-based audit in an acute medical setting (two stages) $n = 229$ medical admissions		Symptoms suggestive of WE: 50% Clinical features suggesting at risk of WE: 30%	3% received optimum dose of thiamine One third received parenteral thiamine as recommended in guidelines
Scottish Emergency Department Alcohol Audit (SEDAA) Group (2008)	Fifteen Emergency Departments in Scotland 985 attendances with serious alcohol problems		Recommended dose of parenteral B vitamins administered to 44% of ED-based treatments[b]	—
McIntosh *et al.* (2005)	Patients undergoing alcohol detoxification on general medical wards Case note audit $n = 70$ 'pre-intervention' (parenteral thiamine indicated in 17 (24%)) $n = 93$ 'post-intervention' [parenteral thiamine indicated in 28 (28%)]	Pre-intervention 75% Post-intervention 40% Intervention: Information from the hospital guideline on the treatment of WKS was integrated into alcohol detox sheet Guidance improved adherence to guideline		
Ward *et al.* (2009)	Web-based study of acute hospital sites in UK: $n = 104$ Treatment of neuro-psychiatric syndromes or a presumptive diagnosis of neuropsychiatric syndromes in hospitals with an alcohol admission protocol	Sixty-two hospitals had protocols 42 hospital did not have protocols	73% of hospitals with protocols 62% of hospital without protocols	17%

The definitions of 'incorrect dose' and 'incorrect duration' were taken from the local protocols, which were derived from the BNF, as NICE guidance was not available at the time.
[a]Percentage of patients prescribed IV thiamine who did not receive it.
[b]44% of an appropriate and eligible group of attendances.

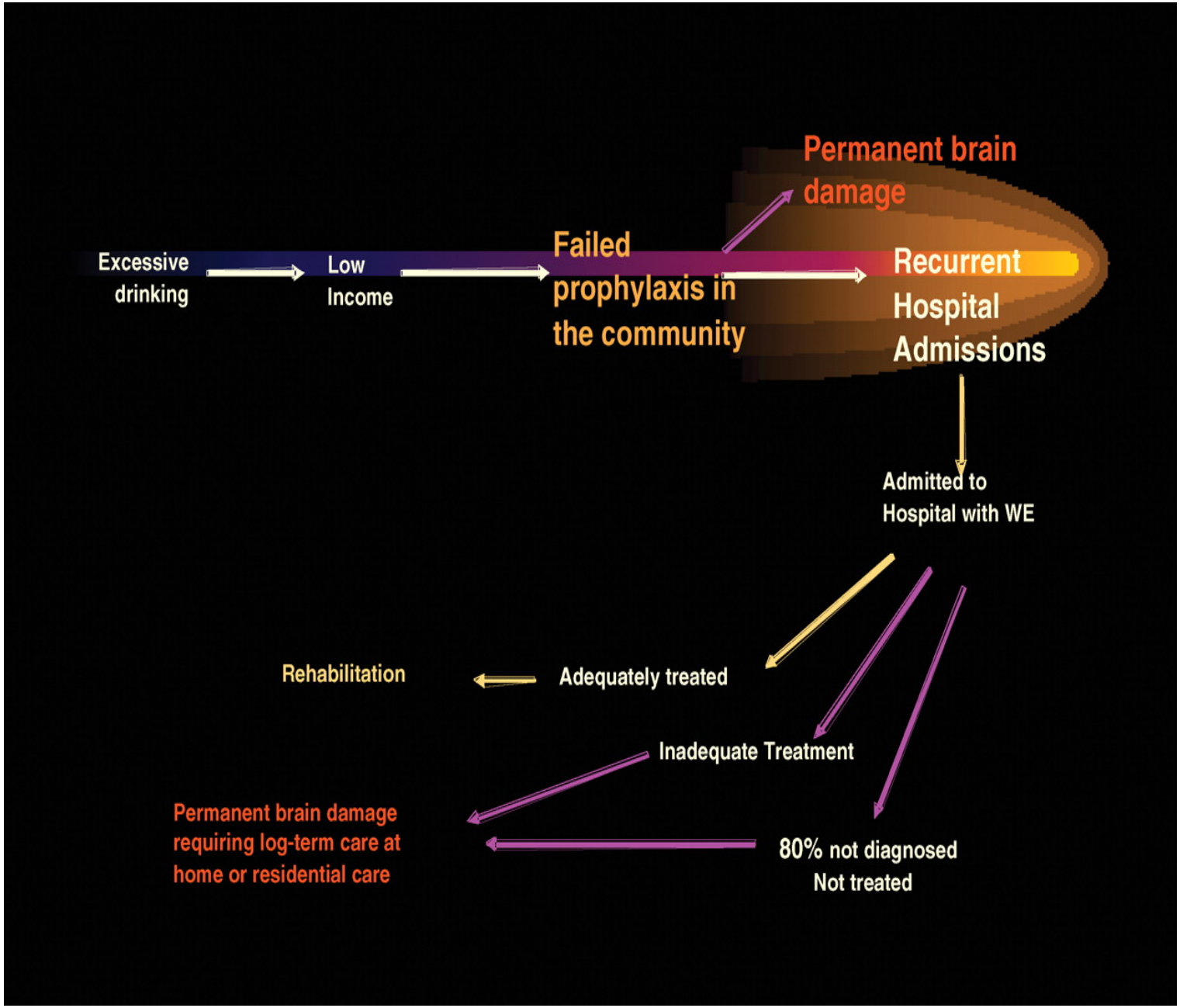
Thomson et al, 2012

Adherence to Guidelines

- Retrospective case note audit of acute medical admissions over 6 month period in Birmingham, England (n=144)
  - ½ of patients had symptoms suggestive of WE and another 30% were at high risk
  - Adherence to prescribing guidelines was 14%
- Prescribers given flow chart with guidelines for thiamine
- Re-audit after 6 months:
  - Small but significant increase in number of patients receiving adequate treatment for WE

Guidelines

- Hospital and treatment centres should have a treatment policy for the prevention and detection of WE
- Local guidelines on the prevention, detection and management of WE should be:
  - clearly written, easily available and audited regularly
- Recording systems should be visible
- All involved healthcare professionals should be trained to have a high degree of suspicion in rrelation to WE


Permanent brain damage
Excessive drinking
Low Income
Failed prophylaxis in the community
Recurrent Hospital Admissions
Admitted to Hospital with WE
Rehabilitation
Adequately treated
Inadequate Treatment
Permanent brain damage requiring log-term care at home or residential care
80% not diagnosed Not treated

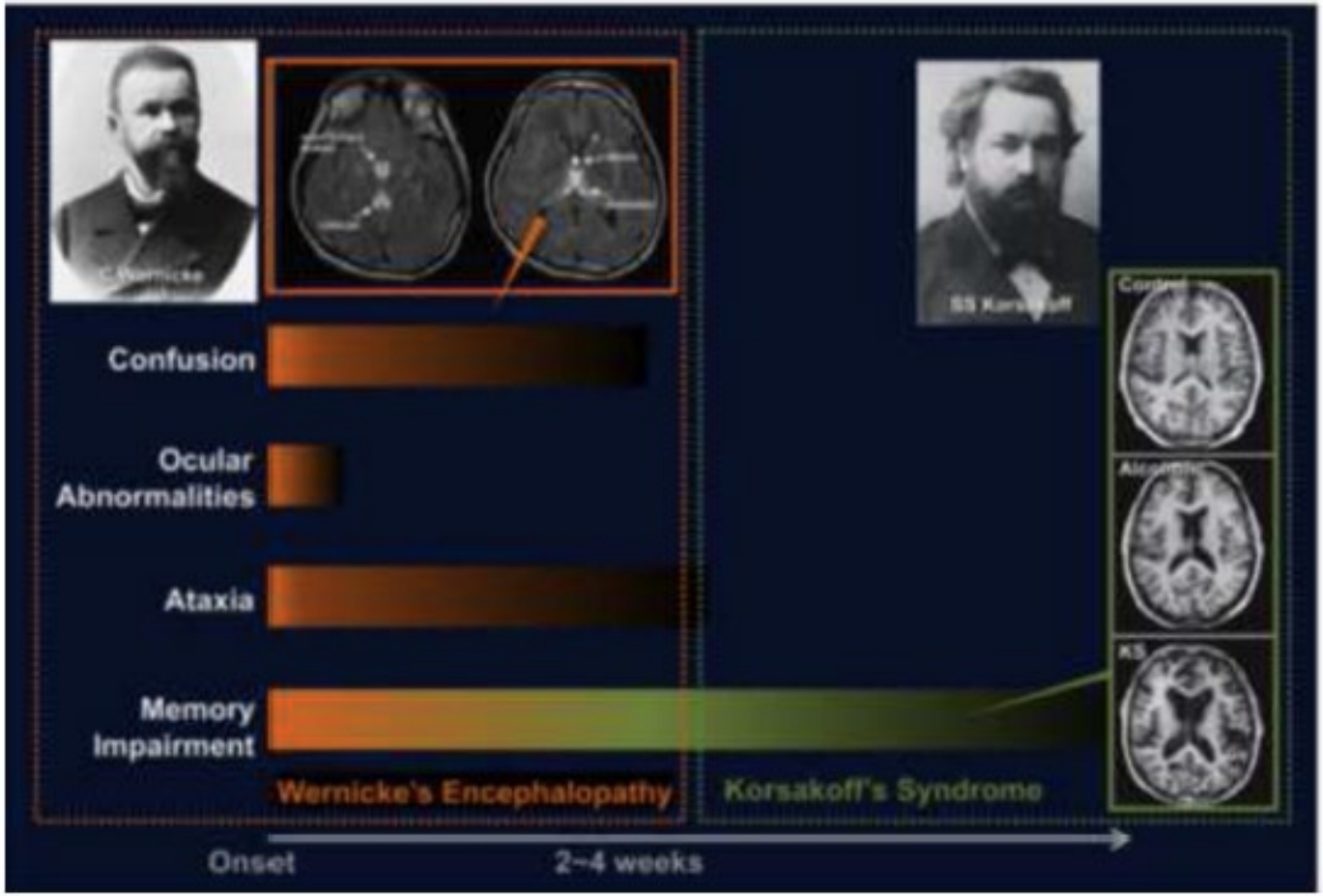


Fig. 1.
Depiction of the temporal progression of signs of Wernicke's Encephalopathy and its radiological signature of hyperintense areas, indicative of edematous tissue, in midline structures, and resolution to global amnesia and permanent structural damaged, most obviously marked by enlarged ventricular and sulcal spaces. Designed by Young-Chul Jung, M.D., Ph.D.

TABLE 1 **The spectrum of neuropsychological deficits seen in alcohol-related brain damage (ARBD)**

Type of deficit	Mild alcohol cognitive impairment	Amnestic syndrome	Severe ARBD with combined neuro-psychological deficit
Orientation	Usually present	Variably absent	Variable
Short-term memory/ immediate recall	Relatively preserved	Relatively preserved	Variably impaired
Recent memory/ delayed recall	Relatively preserved	Impaired with anterograde and retrograde amnesia	Impaired with anterograde and retrograde amnesia
Remote memory	Relatively preserved	Relatively preserved	Variably impaired
Executive function	Mild impairment	Variable impairment: mild to severe	Significantly impaired
General intelligence (IQ)	Preserved	Preserved	Impaired
Visuospatial function	Mildly impaired	Mildly impaired	Impaired
Language function	Relatively intact	Relatively intact	Mildly impaired

Key Points for Decision Makers
Guidelines state that suspected Wernicke's encephalopathy should be treated with 5 days of IV thiamine.
Different admission strategies in at-risk patients were modelled.
Admissions of 5 instead of 2 days may reduce cost per patient by GBP87,000 over 35 years.
Every extra GBP1 spent in acute care is estimated to save GBP6 in future social care costs.

Appl Health Econ Health Policy
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The Long-Term Cost to the UK NHS and Social Services of Different Durations of IV Thiamine (Vitamin B1) for Chronic Alcohol Misusers with Symptoms of Wernicke's Encephalopathy Presenting at the Emergency Department

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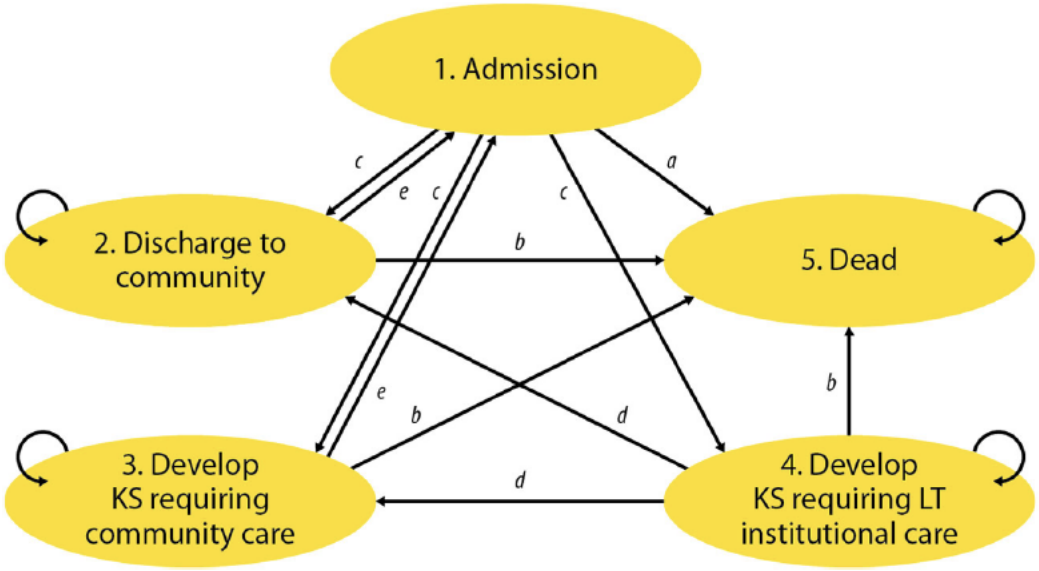
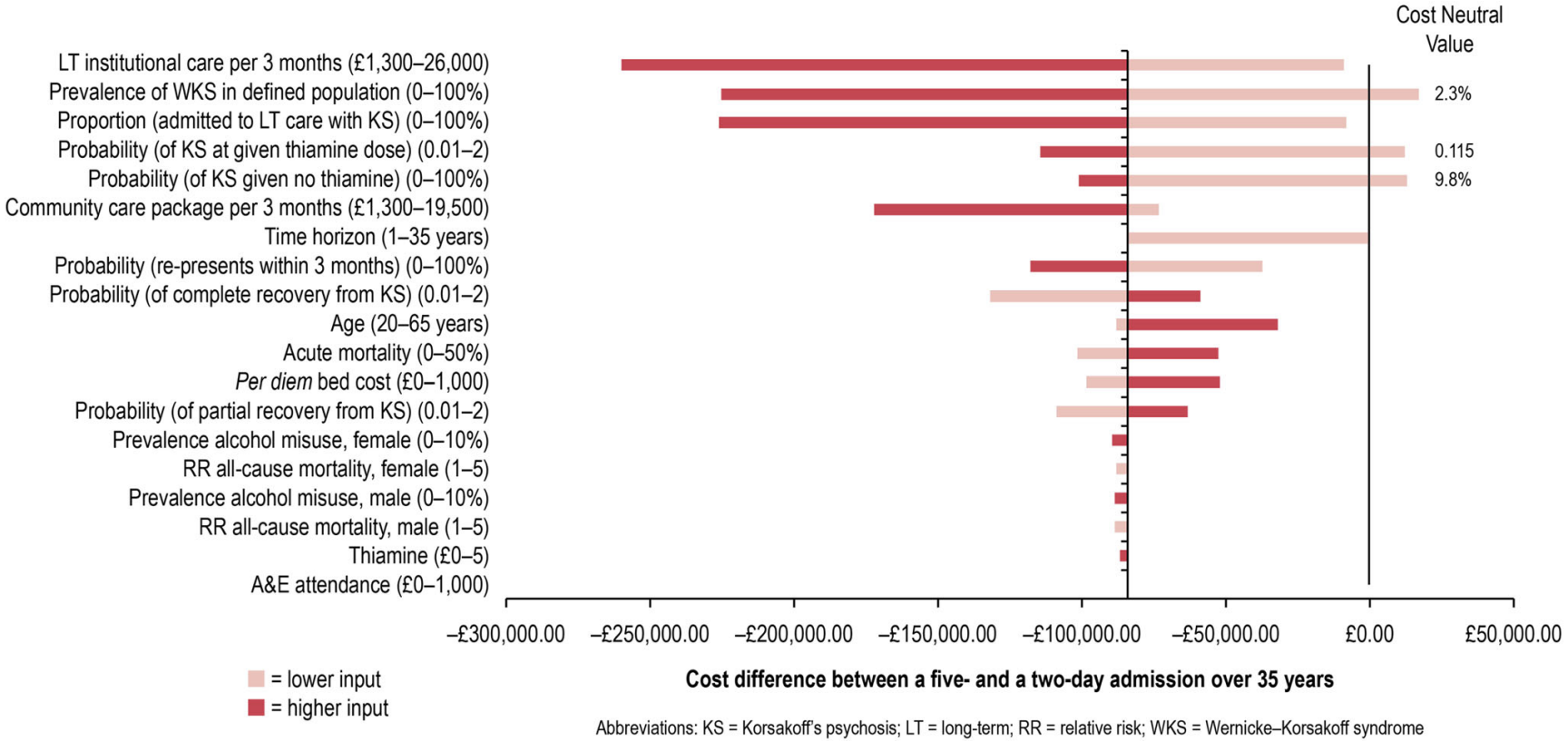


Fig. 1 Schematic of Markov model. *KS* Korsakoff's syndrome, *LT* long-term. *Letters a to e* refer to sets of parameters as described in the text and Table 1



Abbreviations: KS = Korsakoff's psychosis; LT = long-term; RR = relative risk; WKS = Wernicke–Korsakoff syndrome

Thank You

- I am extremely grateful to all below (and many others), with whom I have worked over the past 15 years:
- Dr Allan Thomson
- Dr Irene Guerrini
- Rev Professor Chris Cook
- Dr Iain Smith
- Dr Sameer Jauhar