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INVITED REVIEW

B VITAMIN DEFICIENCY AND NEUROPSYCHIATRIC SYNDROMES IN ALCOHOL MISUSE

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Abstract — Alcohol misuse and alcohol withdrawal are associated with a variety of neuropsychiatric syndromes, some of which are associated with significant morbidity and mortality. B vitamin deficiency is known to contribute to the aetiology of a number of these syndromes, and B vitamin supplementation thus plays a significant part in prophylaxis and treatment. In particular, the Wernicke–Korsakoff syndrome (WKS), due to thiamine deficiency, is a common condition in association with alcohol misuse, and is associated with high morbidity and mortality. Nicotinamide deficiency may result in a rarer condition, alcoholic pellagra encephalopathy, which often has a similar clinical presentation to WKS. This review considers the role of B vitamins in the aetiology and treatment of neuropsychiatric syndromes associated with alcohol misuse, with particular emphasis on WKS.

INTRODUCTION

Alcohol misuse is associated with a range of neuropsychiatric conditions, some of which have a high morbidity and mortality. One of the most serious of these is Wernicke's encephalopathy, which is both common and potentially fatal, as well as being associated with a high level of chronic morbidity amongst survivors, in the form of Korsakoff's psychosis. Wernicke's encephalopathy is due to thiamine deficiency, and the treatment of this condition thus focuses upon rapid replacement of thiamine. Such treatment has the potential to reduce substantially the very significant morbidity and mortality associated with Wernicke's encephalopathy and Korsakoff's psychosis. For a variety of reasons, clinical management of Wernicke's encephalopathy is often confused, inappropriate or entirely neglected. This review evaluates the research literature in this field and makes recommendations for clinical management of such patients. The wider role of B vitamins in neuropsychiatric syndromes associated with alcohol misuse will also be considered.

NEUROPSYCHIATRIC CONDITIONS ASSOCIATED WITH ALCOHOL MISUSE

There are a large number of neuropsychiatric conditions known to be associated with alcohol misuse. Many of these conditions are directly due to alcohol toxicity or withdrawal, but other factors, including malnutrition, also play a part (see Table 1). In addition, there are neurological syndromes secondary to other alcohol-induced disorders (e.g. hepatic encephalopathy) and alcohol-related trauma (e.g. head injury) (see review by Rubino, 1992). This review will focus mainly upon those syndromes in Table 1 which are associated with vitamin deficiencies. However, other syndromes in Table 1, especially delirium tremens, may be difficult to differentiate diagnostically from those that are vitamin related. All of these other syndromes, especially alcohol withdrawal, may also commonly be co-morbid with the vitamin-related syndromes.

There has been a 65% increase in the reported incidence of alcoholic psychoses (ICD-9 code

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Table 1. Neuropsychiatric conditions associated with alcohol misuse

Neuropsychiatric syndrome			Aetiological factors	
Common name	ICD-10*	DSM-IV†	Alcohol	Vitamin deficiency
Intoxication	F10.0 Acute alcohol intoxication	303.00 Alcohol intoxication 291.0 Alcohol intoxication delirium	Alcohol consumption	—
Alcohol misuse	F10.1 Harmful use of alcohol	305.00 Alcohol abuse	Alcohol consumption	—
Alcohol dependence	F10.2 Alcohol-dependence syndrome	303.90 Alcohol dependence	Regular heavy alcohol consumption	—
Alcohol withdrawal	F10.30 Alcohol withdrawal state — uncomplicated	291.8 Alcohol withdrawal	Alcohol withdrawal	—
Alcohol-withdrawal seizures	F10.31 Alcohol withdrawal state — with convulsions	—	Alcohol withdrawal	? Pyridoxine
Delirium tremens	F10.4 Alcohol withdrawal state — with delirium	291.0 Alcohol-withdrawal delirium	Alcohol withdrawal	—
Alcoholic psychosis	F10.5 Alcoholic psychotic disorder	291.3/291.5 Alcohol-induced psychotic disorder	Alcohol intoxication/ withdrawal	—
Wernicke's encephalopathy	G31.2 Degeneration of nervous system due to alcohol‡	—	Chronic heavy drinking	Thiamine
Korsakoff's psychosis	F10.6 Alcoholic-amnestic syndrome	291.1 Alcohol-induced persisting amnestic disorder	Chronic heavy drinking	Thiamine
Alcoholic dementia	F10.73 Alcoholic dementia	291.2 Alcohol-induced persisting dementia	Chronic heavy drinking	—
Cerebellar degeneration	—	—	Chronic heavy drinking	? Thiamine

Marchiafava–Bignami disease	—	—	Chronic heavy drinking	?
Central pontine myelinolysis	—	—	Chronic heavy drinking	?
Alcoholic amblyopia	—	—	Chronic heavy drinking	Thiamine B_{12}
Alcoholic pellagra encephalopathy	—	—	Alcohol misuse	Nicotinamide
Peripheral neuropathy	—	—	Chronic heavy drinking	Thiamine Folate ? Nicotinic acid ? Pyridoxine ? Pantothenic acid
Other	F10.71 Personality or behaviour disorder due to alcohol F10.72 Residual affective disorder due to alcohol F10.74 Other persisting cognitive impairment due to alcohol F10.5 Late onset psychotic disorder due to alcohol F10.8 Other mental and behavioural disorders due to alcohol F10.9 Unspecified mental and behavioural disorder due to alcohol	291.8 Alcohol-induced mood disorder 291.8 Alcohol-induced anxiety disorder 291.8 Alcohol-induced sexual dysfunction 291.8 Alcohol-induced sleep disorder 291.9 Alcohol-related disorder not elsewhere specified	—	—

*World Health Organization (1992). †American Psychiatric Association (1994). ‡Although it would appear that Wernicke's encephalopathy should be classified under G31.2 in ICD-10, this is a broader category, which would also include other forms of damage to the nervous system due to alcohol. There is no specific category for Wernicke's encephalopathy under either ICD-10 or DSM-IV.

Table 2. Finished consultant episodes for ordinary and day case admissions by main diagnosis, National Health Service hospitals, England 1988–1989 to 1993–1994

Year	Alcoholic psychoses ICD-9 code 291	Delirium tremens ICD-9 code 291.0	Alcohol dependence syndrome ICD-9 code 303
1988–1989	2487	438	19 200
1989–1990	3215	565	20 530
1990–1991	3578	631	20 598
1991–1992	4030	720	18 579
1992–1993	4234	699	19 414
1993–1994	4098	750	20 950

Source: Hospital Episode Statistics, Department of Health.

291) (World Health Organization, 1978) in general, and a 70% increase in delirium tremens (code 291.0), specifically in England over the period 1988–1989 to 1993–1994, despite the fact that both admissions for alcohol dependence (see Table 2) and alcohol consumption patterns (Thomas *et al.*, 1994; Bennett *et al.*, 1995) have remained relatively static over this time period.

ICD-9 code 291 'Alcoholic Psychoses' is a rather nebulous grouping which specifically includes Korsakoff's psychosis (code 291.1), but none of the other vitamin-related neuropsychiatric syndromes in Table 1. (In the ICD, it seems that these are meant to be classified elsewhere, with neurological disorders.)

Recent data from Scotland indicate that the majority (83%) of cases of delirium tremens occur in general hospitals (only 17% occurring in psychiatric hospitals) and that a significant proportion (perhaps up to 50%) occur in patients not considered to be alcohol-dependent (CRAG/SCOTMEG Working Group on Mental Illness, 1994) — probably reflecting the poor recording of alcohol histories. Management of these conditions is, therefore, not within the sole ambit of psychiatrists, but is widely applicable to all healthcare providers dealing with patients who misuse alcohol.

WERNICKE–KORSAKOFF SYNDROME

One of the most serious neuropsychiatric conditions associated with alcohol misuse is the Wernicke–Korsakoff syndrome (WKS), which causes significant morbidity and mortality (Victor *et al.*, 1989). Wernicke's encephalopathy is due to thiamine deficiency and is characterized, 'classically' by clouding of consciousness (acute confusion/delirium), ocular signs (nystagmus, ophthalmoplegia), and ataxia. The onset of Wernicke's encephalopathy is commonly, but not always, associated with alcohol withdrawal and may occur in patients who do not misuse alcohol at all (e.g. in those with gastric carcinoma). If high-dose parenteral thiamine is not given urgently, the biochemical abnormalities that thiamine deficiency causes can lead to irreversible brain damage. This damage either leads to death, with mortality rates of 17%–20% being reported, or in 85% of survivors, to the chronic form of the syndrome, Korsakoff's psychosis, characterized by short-term memory loss, but with relative preservation of other intellectual functions. Some 25% of patients developing Korsakoff's psychosis require long-term institutionalization as a result of this selective organic brain damage (Victor *et al.*, 1989).

There are two commonly held fallacies concerning Wernicke's encephalopathy; firstly that it is a rare condition (Torvik *et al.*, 1982; Thomson and Pratt, 1992) and, secondly, that the triad of symptoms originally described by Wernicke in 1881 (ophthalmoplegia, confusion, and ataxia) are invariably present (Harper *et al.*, 1986).

Epidemiology

Unfortunately UK hospital admission data for Korsakoff's psychosis (ICD-9 code 291.1) are not readily available, and Wernicke's encephalopathy is not specifically classified under ICD-9. The proportion of 'alcoholic psychoses' contributed by the WKS, and thus the contribution of this syndrome to the increase in UK admissions for alcoholic psychoses in recent years, is therefore unknown.

The incidence of Korsakoff's psychosis in Glasgow in recent years is reported to have shown a marked increase (Ramayya and Jauhar, 1997). These authors conducted a retrospective analysis of all admissions between 1990 and 1995 in the East End of Glasgow (adult population 160 000) and identified 47 new cases of Korsakoff's psychosis in this 6-year time period. The number of new cases per year were two in 1990,

Table 3. Prevalence of Wernicke's encephalopathy at post-mortem examination (from published studies)

Study	Country	Post-mortem examinations (*n*)	Identified cases of Wernicke's encephalopathy (*n*)	Prevalence (%)
Cravioto *et al.* (1961)	USA	1600	28	1.7
Victor *et al.* (1989)	USA	1539	29	1.9
Jellinger (1976)	Austria	1009*	11	1.1
Victor and Laureno (1978)	USA	3548	77	2.2
Harper (1979)	Australia	2891	51	1.7
Torvik *et al.* (1982)	Norway	8735	70	0.8
Harper (1983)	Australia	4677	131	2.8
Hauw *et al.* (1988)	France	8200	111	1.4
Harper *et al.* (1986)	Australia	285	6	2.1
Lindboe and Loberg (1989)	Norway	6964	52	0.8
Harper *et al.* (1995)	France	256	1	0.4

* Elderly patients with dementia.

seven in 1991, three in 1992, 10 in 1993, 12 in 1994, and 13 in 1995. These figures reveal a rise in incidence from 12.5 per million in 1990 to 81.25 per million in 1995. However, diagnosis in this study was of Korsakoff's psychosis according to 'classical criteria' and the figures would therefore presumably represent a gross underestimate of the total prevalence of brain lesions of the Wernicke–Korsakoff type.

In Australia, hospital admissions for Wernicke's encephalopathy represent a low proportion of total admissions. In a prospective study, Wood *et al.* (1986) found that 32 such patients were admitted to a general hospital over a 33-month period. This represented 0.07% of the total admissions, 1.7% of patients admitted with alcoholism, and 13% of patients admitted with alcoholic psychoses. However, in this study, the presence of ophthalmoplegia was held to be essential to confirm the diagnosis, and this would probably have underestimated the total prevalence (see later). In a retrospective study, Ma and Truswell (1995) found that admissions for WKS to 17 general hospitals in Sydney decreased from 0.032% to 0.023% of total admissions over the period 1978–1993. The decrease may have been attributable to the introduction of thiamine enrichment of bread flour in 1991, although national alcohol consumption also decreased by 24% over the period in question. However, Wernicke's encephalopathy is widely underdiagnosed (see later) and so these figures are also likely to represent an underestimate of the true prevalence.

In necropsy studies representative of the general population, around 1.5% of brains show the morphological lesions of WKS in and near the mamillary bodies. Data from published studies are summarized in Table 3. Harper has also collected unpublished data, which show a prevalence of 0.5–1.3% (Austria), 0.1% (Belgium), 1.0% (Czechoslovakia), 0.4–1.0% (France), 0.3–0.8% (Germany), 0.5% (UK), and 0–1.0% (USA) (Harper *et al.*, 1995).

In alcoholics the condition is, however, much more frequent (Torvik *et al.*, 1982). In a study of 8735 serial post-mortem examinations Torvik found 70 cases of Wernicke's encephalopathy in 561 alcoholics examined — a prevalence of 12.5%. There is also strong evidence that the cerebellar lesions of Wernicke's encephalopathy and those of 'alcoholic cerebellar degeneration' represent the same disease process (Reuler *et al.*, 1985; Victor *et al.*, 1989). In Torvik's study, 26.8% of 567 alcoholics examined showed cerebellar atrophy. It is possible to calculate from the published data that, in this study, approximately 35% of alcoholics examined post-mortem showed the classical lesions of Wernicke's encephalopathy and/or cerebellar atrophy (Torvik *et al.*, 1982; Victor *et al.*, 1989).

In 3.9% of alcoholics (22 patients) examined by Torvik, the cause of death was diagnosed, post-mortem, to be as a direct result of an acute episode of Wernicke's encephalopathy (Torvik *et al.*, 1982). In Harper's studies of patients with Wernicke's encephalopathy, over 20% died sud-

denly and unexpectedly. Harper also noted that lesions described histopathologically as being 'chronic' Wernicke's encephalopathy may also cause sudden death (Harper, 1979; Harper *et al.*, 1986).

Aetiology

The involvement of thiamine deficiency in the aetiology of WKS was suspected over 50 years ago. Bowman *et al.* (1939) showed some evidence of a beneficial effect of parenteral thiamine in the treatment of Korsakoff's psychosis with 'acute onset'. These patients would possibly now be diagnosed as suffering from Wernicke's encephalopathy. At about the same time, Alexander (1939) showed that pigeons fed on a thiamine-deficient diet developed lesions identical in distribution, morphology, and histology to those found in human Wernicke's encephalopathy. Later, de Wardener and Lennox (1947) showed that in prisoners of war on a grossly deficient diet, the general incidence of cases of Wernicke's encephalopathy coincided in time with the incidence of classical beriberi. There was also a close association in individual cases (79%) with classical beriberi, and the syndrome responded to treatment with thiamine.

Jollife *et al.* (1941) published a report of a series of 27 cases of Wernicke's encephalopathy and noted that, amongst those who recovered, the development of Korsakoff's psychosis was 'the rule'. Furthermore, they noted that Korsakoff's psychosis generally did not respond to thiamine supplementation (Jollife *et al.*, 1941). Malamud and Skillicorn (1956) suggested that, in view of the clinical association and the similar distribution of the underlying lesions, Wernicke's encephalopathy and Korsakoff's psychosis were manifestations of the same disorder, differing only in the acuteness or chronicity of the underlying disease process. The full history of the development of the understanding of the link between Wernicke's encephalopathy and Korsakoff's psychosis, and the aetiology of WKS, have been reviewed by Lishman (1981).

WKS has since been shown to be associated with thiamine deficiency (Butterworth *et al.*, 1993), and the activity of thiamine-dependent enzymes in the brain in Wernicke's encephalopathy is known to be reduced by 70–97% (Tallaksen *et al.*, 1993). However, thiamine deficiency and reduced activity of the dependent enzymes are also seen in alcoholics without WKS (Lavoie and Butterworth, 1995).

WKS is often precipitated, in those who are alcohol-dependent, by the stress of an intercurrent illness or it can also develop during or following treatment of alcoholic seizures or delirium tremens — conditions placing increased demands on already depleted thiamine stores. For example, Victor *et al.* (1989) found that, in a group of 50 hospitalized alcoholic patients with Korsakoff's psychosis, the condition began in 38% of cases with an attack of delirium tremens. Similarly, in patients dying acutely during an episode of delirium tremens, brainstem lesions differing only quantitatively from those of Wernicke's encephalopathy have been found (Anonymous, 1981). Because of the similarity, in both histopathological and clinical presentations (see later), a number of authors have postulated that these two conditions may represent part of the same continuum (Anonymous, 1981; Victor *et al.*, 1989).

There is a specific topographic pattern of lesions in WKS which focuses on periventricular regions including the mamillary bodies [which act as a relay centre between hippocampal and thalamic nuclei in one of the two memory circuits (Meyer, 1958)], other hypothalamic structures, periventricular thalamic nuclei, and structures in the floor of the fourth ventricle (Thomson and Pratt, 1992). Involvement of the dorso-medial nucleus of the thalamus appears to be particularly associated with memory disturbance (Victor, 1964).

It is possible that a minority of patients diagnosed clinically as having Korsakoff's psychosis may in fact have a form of alcoholic dementia (Cutting, 1978; Jacobson and Lishman, 1987). As it currently appears that alcoholic dementia is not due to thiamine deficiency (see later), this may suggest that there is in fact a degree of aetiological heterogeneity within the diagnosis of Korsakoff's psychosis.

Clinical presentation

Harper, in a review of published pathological studies, found that only 10% of patients with Wernicke's encephalopathy had the full classical triad of clinical signs. Thus, 23% had ataxia, 29% had ocular signs and 82% presented with mental changes i.e. confusion, drowsiness, obtundation,

pre-coma, and coma (Harper *et al.*, 1986). It is also now believed that Wernicke's encephalopathy can evolve as 'minor' episodes of 'subclinical' encephalopathies in which all of the classical features are absent (Reuler *et al.*, 1985; Blansjaar and Van Dijk, 1992). Because of the very non-specific presentation of WKS in clinical practice, and the wide differential diagnosis that exists, ante-mortem diagnosis is reported to occur in only around 5% of cases (Torvik *et al.*, 1982).

In addition to the classical signs of Wernicke's encephalopathy, patients may also present with a history of alcohol misuse and otherwise unexplained hypothermia and hypotension (Koeppen *et al.*, 1969). Hypothermia may also occur in the absence of hypotension (Philip and Smith, 1973; Hunter, 1976). Response to parenteral B vitamins apparently occurs rapidly in some cases (Ackerman, 1974; Reuler *et al.*, 1985; Lindberg and Oyler, 1990), but body temperature may take up to 2 weeks to return to normal (Hansen *et al.*, 1984).

ALCOHOLIC PELLAGRA ENCEPHALOPATHY

Alcoholic pellagra, first recognized in 1869, is due to deficiency of niacin (and possibly other B vitamins) in association with chronic alcohol misuse. The signs and symptoms are generally similar to those seen in 'endemic' pellagra, and in acute and severe deficiency they may include an encephalopathic syndrome characterized most frequently by confusion, oppositional hypertonus, and myoclonus (Serdaru *et al.*, 1988). Cogwheel rigidity and grasping and sucking reflexes (Jollife *et al.*, 1940; Serdaru *et al.*, 1988), hallucinations, insomnia, tremor, ataxia, and urinary and faecal incontinence (Ishii and Nishihara, 1981) are also commonly seen. Peripheral neuropathy, seizures, anxiety, depression, excitement, and neurasthenia may also occur (Ishii and Nishihara, 1981). This syndrome has been termed 'alcoholic pellagra encephalopathy'.

Alcoholic pellagra encephalopathy is much less common than WKS, with a prevalence of only 0.003% in one series of post-mortem examinations (Hauw *et al.*, 1988). However, it has been suggested that routine multiple vitamin therapy may have significantly reduced the incidence of the syndrome in the USA and UK since the 1950s (Lishman, 1981). There is also evidence that it may be subject to even greater under diagnosis. In one survey of 74 post-mortem examinations of alcoholic patients who died in hospital, 20 (27%) were found to have neuropathological features of pellagra (Ishii and Nishihara, 1981).

The differential diagnosis from other neuropsychiatric syndromes associated with alcohol misuse can be difficult. For example, a diagnosis of delirium tremens is often made (Ishii and Nishihara, 1981). Furthermore, alcoholic pellagra encephalopathy occurs not infrequently in combination with other alcoholic encephalopathies, and treatment with thiamine and pyridoxine without niacin appears to aggravate or precipitate the condition (Serdaru *et al.*, 1988). Characteristic microscopic changes assist with diagnosis at post-mortem examination, notably chromatolysis of neurones in the central nervous system (CNS), especially in the pons (Ishii and Nishihara, 1981; Hauw *et al.*, 1988).

Alcoholic pellagra encephalopathy responds readily to treatment with nicotinic acid (Cleckley *et al.*, 1939), although a significant mortality is still reported (Jollife *et al.*, 1940; Gottlieb, 1944). In one published case report, treatment with i.v. B-complex vitamins (including both thiamine and nicotinamide) led to the resolution of the pellagra encephalopathy, but did not prevent the development of Wernicke's encephalopathy (Teare and Pollock, 1993). The exact dose of vitamins given was not reported, but it would appear that the dose of thiamine was insufficient as prophylaxis against Wernicke's encephalopathy, whilst the dose of nicotinamide was sufficient to treat the pellagra encephalopathy. This would suggest that it may be important that the treatment of alcoholic pellagra encephalopathy should include high doses of parenteral thiamine as well as nicotinamide.

OTHER VITAMIN-RELATED NEUROPSYCHIATRIC CONDITIONS ASSOCIATED WITH ALCOHOL MISUSE

As discussed above, alcoholic cerebellar degeneration may well be due to thiamine deficiency, and may actually be a part of WKS. Peripheral neuropathy is also commonly associated with WKS, and was originally considered by Korsakoff to be a part of his 'psychosis polyneuritica'. However, it also commonly occurs separately from WKS and may be caused by folate deficiency

(Gimsing *et al.*, 1989) and possibly pyridoxine, pantothenic acid, or nicotinic acid deficiency as well as (more commonly) thiamine deficiency (Fennelly *et al.*, 1964). It has also been suggested that, in some patients without thiamine deficiency, peripheral neuropathy may develop as a result of an alcohol-induced defect in thiamine utilization (Paladin and Perez, 1987).

Marchiafava–Bignami disease, central pontine myelinolysis, and alcoholic amblyopia are all rare, but have also been thought to be possibly due to nutritional deficiencies associated with alcohol misuse. These disorders have been reviewed by Lishman (1987*b*).

Marchiafava–Bignami disease is associated with CNS demyelination particularly affecting the corpus callosum. It is very rare, and Victor and Laureno (1978) found a prevalence of only 0.06% (two cases) in their series of 3548 post-mortem examinations. Although it has been suggested that there may be a nutritional origin (Lishman, 1987*b*), this is not universally agreed (Delmas-Marsalet *et al.*, 1967), and at least one published case report provides evidence of a lack of response to i.v. vitamins, including high doses of thiamine (Ikeda *et al.*, 1989).

Central pontine myelinolysis was first described almost 40 years ago (Adams *et al.*, 1959). It may be associated with Wernicke's encephalopathy both in the presence (e.g. Cole *et al.*, 1964; Rodriguez and Hankey, 1987) and absence (e.g. Bergin and Harvey, 1992) of alcohol misuse. Post-mortem examination reveals demyelination of the pons, and the disease is usually thought to be very rare. Victor and Laureno (1978) found a prevalence of only 0.3% (nine cases) in a series of 3548 post-mortem examinations. However, one post-mortem survey revealed that demyelination is not confined to the pons, and the authors were able to identify 58 cases of central pontine and/or extrapontine myelinolysis (a prevalence of 1.0%) in a series of 5926 brain autopsies (Gocht and Colmant, 1987). A nutritional basis has been suggested, in view of the frequent association with malnutrition (Cole *et al.*, 1964), but more recently the sudden correction of hyponatraemia has been implicated (see discussion by Hankey in Rodriguez and Hankey, 1987, and also Norenberg *et al.*, 1982; Illowsky and Laureno, 1987; Brunner *et al.*, 1988), and an association with hypokalaemia has also been observed (Bähr *et al.*, 1990). Experimental work with dogs has also supported the possible importance of rapid reversal of the hyponatraemia (Laureno, 1983). Neither malnutrition nor hyponatraemia are invariable features of this condition, and treatment with large doses of B vitamins appears to be ineffective (Wright *et al.*, 1979). Possibly, thiamine deficiency may make the myelin sheaths more sensitive to sudden changes in serum sodium (Bergin and Harvey, 1992).

Alcoholic amblyopia presents as a painless bilateral loss of vision in association with alcohol misuse. The majority of patients are also smokers. A variety of B vitamin deficiencies have been implicated in the aetiology, although thiamine appears to be the most important. The visual impairment has been shown to respond to treatment with thiamine or B-complex vitamins, even, in some cases, when alcohol misuse continues (Carroll, 1944, 1945; Primo, 1988). In one report of two cases, reduced transketolase activity has been demonstrated (Dreyfus, 1965).

It has been suggested that thiamine deficiency contributes to the aetiology of alcoholic dementia, but serum thiamine correlates poorly with cognitive deterioration (Molina *et al.*, 1994), and is therefore now not thought to play a major aetiological role in this condition (Lishman, 1987*a*). However, the failure to correlate current thiamine status with cognitive deterioration does not preclude the influence of earlier damage attributable to thiamine deficiency. It is also important to remember that thiamine utilization, rather than thiamine status *per se*, is the critical aetiological factor.

A causal role of thiamine deficiency in delirium tremens has now been excluded (Lishman, 1987*a*), although this condition may often be confused diagnostically with Wernicke's encephalopathy, and the two conditions may also frequently coexist (see earlier).

There is some evidence that pyridoxine deficiency may increase the risk of alcohol withdrawal fits, but the causal relationship does not appear to be well established (see later). It has also been suggested that i.v. pyridoxine produces dramatic reversal of alcoholic intoxication, but numerous studies have failed to replicate this finding (see review by Bonjour, 1980).

A wider range of neuropsychiatric conditions are also associated with B vitamin deficiencies,

Table 4. Neuropsychiatric conditions associated with B vitamin deficiency

B Vitamin	Neuropsychiatric condition
Thiamine (B_1)	Wernicke–Korsakoff syndrome
	Leigh's disease (subacute necrotizing encephalomyopathy)
	Neurasthenia
	Depression
	Peripheral neuropathy
Biotin	Anorexia, lassitude, sleeplessness
Pantothenic acid	Fatigue, irritability
	Peripheral neuropathy
Pyridoxine (B_6)	Irritability, confusion and lethargy
	Depression
	Seizures (in infants)
	Peripheral neuropathy
B_{12}	Neurasthenia
	Depression
	Psychosis
	Dementia
	Seizures
	Subacute combined degeneration of the cord
Choline	? Deficiency does not occur
Folate	Depression
	Dementia
	Peripheral neuropathy
Nicotinic acid	Neurasthenia (in early stages)
	Depression
	Psychosis
	Acute organic brain syndrome
	Seizures
	Spastic paralysis, ataxia, tremor
	Retrobulbar neuritis
	Deafness
	Peripheral neuropathy
Riboflavin	Lethargy, low mood, hypochondriasis

but are not necessarily associated with alcohol misuse. These are listed in Table 4 (see also Lishman, 1987*b*).

Given the high prevalence of B vitamin deficiencies in alcohol dependence (see below), it may well be that more attention should be paid to the detection of these conditions in patients admitted for alcohol withdrawal.

B VITAMIN DEFICIENCY IN ALCOHOL MISUSE AND DEPENDENCE

B vitamin deficiencies are common in alcoholics (Thomson *et al.*, 1987). Thiamine (B_1) deficiency has been reported in 30–80% of alcoholics, folate deficiency in 60–80%, pyridoxine (B_6) deficiency in 50% (Thomson *et al.*, 1987), and riboflavin (B_2) deficiency in 17% (Thomson *et al.*, 1996). Whilst much less common, nicotinic acid deficiencies have also been reported (Thomson *et al.*, 1987).

A complete exposition on the role of the B vitamins is beyond the scope of this review. However, thiamine, pyridoxine, riboflavin, and nicotinamide act as coenzymes and are involved in glucose and lipid metabolism and the production of amino acids and glucose-derived neurotransmitters (Tower, 1956, 1958, 1976; Greenwood *et al.*, 1985*a*; Thomson *et al.*, 1987, 1994; Thomson, 1990; Thomson and Pratt, 1992). The brain depends on an adequate supply of glucose both as an energy source and as a donor of carbon fragments for protein, neurotransmitter and lipid biosynthesis. Glucose utilization is B vitamin-dependent and it is likely that a breakdown in this complex metabolic process is a major factor in the production of B vitamin-deficient brain damage (Pratt *et al.*, 1985; Thomson *et al.*, 1987; Thomson and Pratt, 1992).

The consequences of B vitamin deficiencies on the central and peripheral nervous systems are shown in Table 4. Given the overlap in symptomatology, and the fact that alcoholics are commonly deficient in a number of the B vitamins (Thomson *et al.*, 1987), most authorities advocate the use of B-complex vitamins in the management of neuropsychiatric conditions associated with alcoholism (Anonymous, 1979, 1981, 1991; Guthrie and Elliot, 1980; Greenwood *et al.*, 1985*b*; Thomson and Pratt, 1992).

Thiamine

The three major thiamine-dependent enzyme systems are pyruvate dehydrogenase, transketolase, and 2-oxo-glutarate dehydrogenase. Pyruvate dehydrogenase is involved in the breakdown of pyruvate to acetyl coenzyme A, which feeds into the Krebs cycle, and is thus involved in energy production. Transketolase is involved in the pentose phosphate pathway, the maintenance of myelin sheaths in the nervous system, lipid and glucose metabolism, and branched chain amino acid production. 2-Oxo-glutarate dehydrogenase is involved in the tricarboxylic acid cycle, and synthesis of glucose-derived neurotransmitters [acetylcholine, γ-amino butyric acid (GABA) and glutamate] (Thomson *et al.*, 1987; Thomson and Pratt, 1992).

A considerable amount of research has recently been conducted on transketolase, a key enzyme involved in glucose metabolism within the CNS (Pratt *et al.*, 1985; Thomson *et al.*, 1987, 1994; Thomson and Pratt, 1992).

The apoenzyme of transketolase apparently exists in two (or more) forms in different patients. One component apoenzyme has its thiamine diphosphate (TDP) coenzyme firmly bound, while the other variant is a smaller molecule which is inactive without added TDP, for which it has reduced affinity (Pratt *et al.*, 1985). This could represent a genetic variant with altered TDP binding predisposing the subject to brain damage due to thiamine depletion. Equally, the transketolase protein may be damaged by acetaldehyde or reactive oxygen species; the fragments resulting in altered binding with TDP. Under these circumstances, there would also be an increased requirement for thiamine, hence predisposing malnourished subjects to thiamine deficiency and, subsequently, brain damage. As thiamine receptor sites on the apoenzyme molecule become vacant, due to thiamine depletion, the molecule also becomes unstable and vulnerable to irreversible damage. It may, however, be activated at non-physiological levels of thiamine diphosphate, i.e. at levels which cannot be achieved with orally administered thiamine (Pratt *et al.*, 1985; Thomson *et al.*, 1994). This may explain the wide inter-patient variation in amounts of thiamine required to resolve the symptomatology of Wernicke's encephalopathy (Blass and Gibson, 1977).

It was thought that the low affinity variant of transketolase might be a mediator of genetic susceptibility to Wernicke–Korsakoff psychosis (Blass and Gibson, 1977; Martin *et al.*, 1993). However, although this enzyme variant is seen commonly in patients with WKS, it is also found in alcoholics without WKS, unaffected sons of alcoholics (Mukherjee *et al.*, 1987), and (less commonly) in the normal population (Greenwood *et al.*, 1984). A comparison of DNA from two WKS patients and two controls revealed no coding differences specific to the WKS subjects (McCool *et al.*, 1993).

Pyridoxine

Pyridoxine (B_6) is unique amongst the B-complex vitamins in that it is the only member in which deficiency, or interference with its function, commonly results in epileptiform seizures in all mammalian species, including man (Tower, 1956, 1958, 1976). Seizure disorders associated with inadequate B_6 nutrition relate to the function of the vitamin as a coenzyme for glutamic acid decarboxylase (GAD), the enzyme which synthesizes the inhibitory neurotransmitter GABA from glutamic acid (Tower, 1976). In nutritional seizure states, clinical response and normalization of electroencephalograms have been shown to occur within minutes of administration of parenteral pyridoxine — demonstrating a functional interference with an essential metabolic step which can be promptly reversed or corrected by appropriate measures (Tower, 1956, 1958, 1976). We might speculate, therefore, that pyridoxine deficiency could contribute to the aetiology of alcohol-withdrawal seizures, and there is some evidence in support of this contention.

In one early study, five patients with 'rum fits' showed greater evidence of pyridoxine deficiency than two patients with alcoholism and epilepsy, six patients with alcoholism who had suffered no fits, and one normal control (Lerner *et al.*, 1958). In another study, only one out of 23 male alcoholics treated with 100 mg of pyridoxine suffered a withdrawal fit, as compared with seven out of 23 not given this treatment. Another 20 patients studied by the same author were all given pyridoxine, and none of them suffered withdrawal fits (Lunde, 1960). The sample sizes in these studies were very small, but we have not been able to find any larger or more recently published studies.

Vitamin storage

The water-soluble vitamins are not extensively stored by the body; for example, the body stores around 25–30 mg thiamine, principally in the heart, brain, liver, and kidneys. In healthy individuals, daily turnover is approximately 1 mg and a regular intake is required to maintain these reserves (McCormick, 1988). Deficiency can present within 2–3 weeks of intake ceasing (Velez *et al.*, 1985). In chronic alcoholics, this problem is compounded for a number of reasons, including inadequate diet, reduced absorption, increased metabolic demands, and reduced hepatic storage (Thomson and Majumdar, 1981; Greenwood *et al.*, 1985*b*). Whilst research has concen-

trated on the storage, utilization, and role of thiamine, the other B vitamins are known to be adversely affected in alcoholics in a similar way (Thomson *et al.*, 1996).

TREATMENT OF B VITAMIN DEFICIENCY AND WKS ASSOCIATED WITH ALCOHOL MISUSE

In treating B vitamin-related neuropsychiatric conditions associated with alcoholism, in view of the high morbidity and mortality, the aim must be to restore CNS B vitamin levels as rapidly as possible in order to correct the concomitant metabolic imbalance. Similar considerations will apply to the prophylaxis of neuropsychiatric conditions associated with alcohol misuse and withdrawal. Although most research has focused on thiamine and WKS, similar concerns relate to other B vitamins (see Thomson *et al.*, 1996), and it would therefore appear reasonable to assume that the same general principles should apply to them too.

This review will focus upon B vitamin supplementation, and other sources should be consulted regarding the general management of alcohol withdrawal (e.g. Turner *et al.*, 1989; Edwards *et al.*, 1997). However, it is important to note that a large carbohydrate load, administered parenterally (e.g. as an i.v. glucose infusion) or by mouth will increase the thiamine requirement and may thereby precipitate or exacerbate Wernicke's encephalopathy (see e.g. Lonsdale, 1978). Similarly, oral hypoglycaemic agents may precipitate Wernicke's encephalopathy (Kwee and Nakada, 1983).

In order to understand how this rapid restoration of CNS vitamin levels may best be achieved, we must consider research evidence in respect of route of administration (oral vs parenteral), frequency and dosage of administration and the safety profile of the vitamins as commercially available. This research evidence will then be compared against current practice in the UK and will be used to formulate recommendations for good clinical practice in the prevention and treatment of WKS.

Parenteral vs oral B vitamin supplementation

Absorption from the gastrointestinal tract. Thiamine transport across the intestinal wall in man is mediated via active, saturable, stereospecific and sodium-dependent transport mechanisms. Kinetic studies have shown that, in healthy volunteers, a 10-mg dose of thiamine maximizes oral absorption i.e. increasing a single oral dose above this level has no significant effect on plasma or cumulative urinary thiamine levels under test conditions. The maximum amount of thiamine absorbed from single oral doses of 10 mg or greater would appear to be between 4.3 mg and 5.6 mg (Thomson *et al.*, 1970).

Absorption of thiamine appears to be independently affected by ethanol and malnutrition (Thomson *et al.*, 1970; Greenwood *et al.*, 1985*b*; Thomson, 1990). In abstemious malnourished alcoholics, the oral absorption of thiamine is extremely variable (some patients showing little, or no, absorption). However, absorption is approximately 30% of that in healthy individuals i.e. a maximum of 1.5 mg of thiamine can be absorbed from a single oral dose of 10 mg or greater. In the presence of alcohol, thiamine absorption is further impaired. In one-third of patients, a further 50% reduction in absorption was found with concomitant administration of alcohol and thiamine (Thomson *et al.*, 1970).

Research would thus suggest that only 0.8 mg or less of an oral dose of thiamine might be absorbed in malnourished patients who have recently been drinking and in some patients the amount absorbed is extremely low. The daily thiamine requirement is approximately 1–1.6 mg in healthy individuals. Presumably the requirement is higher in patients with Wernicke's encephalopathy, although little or nothing is known about how much thiamine must be absorbed in order to reverse or arrest the condition. Neither has there apparently been any research into the possible advantages of multiple daily dosage of oral thiamine in prophylaxis against Wernicke's encephalopathy. However, where a therapeutic dose is required, the rapidity of the requirement for thiamine repletion would appear to preclude this option anyway.

Given these considerations, oral thiamine supplementation in alcoholics (particularly if they continue to drink) is likely to be quite inadequate. It is therefore not surprising that cases of Wernicke's encephalopathy have been described in alcoholics taking high-dose B vitamin supplementation orally (Chataway and Hardman, 1995). It is perhaps surprising, however, that some

patients apparently do show clinical improvement on oral supplements (Meyer *et al.*, 1985). Furthermore, in one study of alcoholic patients, an oral regimen of 50 mg thiamine daily for 5 days did elevate erythrocyte levels of thiamine diphosphate (Baines *et al.*, 1988). However, malnourished subjects were excluded from the study group and the levels of thiamine were elevated more rapidly in a comparison group who were given 250 mg daily i.m.

Transport across the blood–brain barrier. Thiamine has active and passive transport mechanisms across the blood–brain barrier. The active mechanism is both rate-limited and saturable at low thiamine levels (Greenwood *et al.*, 1985*b*). Active uptake occurs at a maximum rate of approximately 0.3 μg/h/g of brain tissue. This rate is comparable to that calculated for brain thiamine turnover, suggesting that thiamine transport may be just sufficient to meet normal cerebral requirements and that there may exist very little excess capacity of the system (Butterworth, 1995). Rapid correction of CNS vitamin levels, therefore, requires a high plasma : CNS concentration gradient to be established such that passive diffusion is encouraged.

A number of published studies comparing the effects of oral vs parenteral vitamin supplementation in chronic alcoholics have demonstrated the beneficial role of high-dose parenteral therapy in terms of restoration of CNS levels (Baker and Frank, 1976; Thomson *et al.*, 1983). Baker and Frank (1976) studied the absorption, utilization, and clinical effectiveness of various thiamine derivatives. They showed that, in contrast to parenterally administered water-soluble thiamines (thiamine hydrochloride and thiamine pyrophosphate), oral administration of water-soluble thiamine neither elevated thiamine activity in cerebrospinal fluid nor restored transketolase activity to normal in alcoholics with thiamine deficiency.

Thomson (1969) and Thomson *et al.* (1983) evaluated thiamine supplementation in six thiamine-deficient alcoholic patients with Wernicke's encephalopathy. Patients initially received 50 mg of thiamine hydrochloride orally followed 24 h later by 50 mg of thiamine propyl disulphide (a fat-soluble form which behaves like a parenteral presentation). This latter product was in development in Japan in the 1960s but has never been commercially available as a pharmaceutical product. It is, however, available 'over the counter' as a food supplement in the USA. Blood and CNS thiamine and pyruvate levels were measured by the above authors post-treatment. Oral thiamine hydrochloride had little or no effect on either CNS or blood vitamin status. Pyruvate levels in blood and CNS (a marker of carbohydrate metabolic degradation) only fell significantly following administration of bioavailable thiamine. The authors also noted a marked improvement in clinical symptoms (ataxia, confabulation, ocular palsy, etc) following repeated therapy with the bioavailable form of thiamine, but not with oral thiamine hydrochloride.

Frequency of administration of parenteral B vitamin supplements

Blood thiamine levels fall to baseline values between 6 and 24 h after administration of the bioavailable form (Thomson *et al.*, 1983). Unpublished data using radiolabelled thiamine in deficient alcoholics have also demonstrated that thiamine plasma levels decline to 20% of peak values within 2 h of parenteral administration (Thomson, 1969). Thus, the 'window' for passive diffusion to occur appears to be relatively short. In order to restore CNS B vitamin levels in patients with WKS, parenteral vitamins should therefore be administered twice or three times daily.

Dosage of parenteral B vitamin supplements

No formal, dose-ranging, placebo-controlled studies have been conducted on the use of parenteral B-complex vitamins in alcoholics. Knowledge concerning the appropriate dosage is, therefore, largely based on data from uncontrolled trials and empirical clinical practice. In reviewing these publications, it is also important to distinguish those circumstances where the vitamin supplements were being used prophylactically, and those where they were being used in treatment of established or suspected WKS.

Prophylaxis. One study of 12 patients (Majumdar, 1980) has described a prophylactic regime of one pair of Parentrovite ampoules of high-potency parenteral B-complex vitamins once daily for 5 days in 'at-risk' alcoholics undergoing detoxification. The regimen was apparently clinically effective in preventing the development of WKS, and transketolase activity was restored to normal in

seven patients with marginal/low levels of activity. Parentrovite was similar to the only high-potency parenteral B complex preparation currently available in the UK (Pabrinex). Both preparations contain(ed) 250 mg of thiamine hydrochloride in addition to other B vitamins (4 mg riboflavin, 50 mg pyridoxine hydrochloride, and 160 mg nicotinamide) and 500 mg ascorbic acid.

Another study suggested that one pair of ampoules of high-potency parenteral B-complex vitamins once daily for 5 days did not restore vitamin status as measured by the activity of thiamine-dependent enzymes (Brown *et al.*, 1983). A later study, measuring thiamine diphosphate directly, showed that a similar regime, using i.m. administration, was effective (Baines *et al.*, 1988). The latter study seems therefore to suggest that such a regime might be effective prophylactically, although the former study did not. However, the discrepancy might be explicable on the basis that normal thiamine levels may still be associated with impaired utilization of thiamine due to a damaged apoenzyme.

Treatment. Data are extremely limited on dosage and duration of therapy in this condition. However, low-dose parenteral therapy does not appear to be reliably effective in preventing morbidity and mortality. Doses of between 100 mg and 250 mg of thiamine/day apparently may not restore vitamin status (Brown *et al.*, 1983), or improve clinical signs (Tallaksen *et al.*, 1992) or prevent death (Harper *et al.*, 1986). Despite this, low doses are often used, and are sometimes observed to be rapidly effective (Guido *et al.*, 1994), albeit in other cases recovery may be delayed and incomplete (Cole *et al.*, 1969; Evans *et al.*, 1985; Heye *et al.*, 1994; Chataway and Hardman, 1995).

Depending upon the severity of the presenting neuropsychiatric condition, and the perceived certainty of the diagnosis of Wernicke's encephalopathy, a number of effective dosage regimens have been described. These regimes have included two pairs of i.v. high-potency B-complex vitamins once or twice daily for 3–10 days (Hoher, 1962; Von Hackstock, 1962; Victor *et al.*, 1989). [The paper by Von Hackstock (1962) refers to diagnoses of 'delirium tremens', although the delirium described was more probably a result of Wernicke's encephalopathy.] In confirmed Wernicke's encephalopathy, doses of up to 1 g of thiamine may be required, initially, to achieve a clinical response (Nakada and Knight, 1984; Lindberg and Oyler, 1990). However, the Parentrovite and Pabrinex Data Sheets recommend, respectively, two to four pairs i.v. high-potency ampoules 4- to 8-hourly for 2 days, with one pair i.v. high-potency ampoules to be given subsequently for 5–7 days and two to three pairs of ampoules 8-hourly for an unspecified length of time, regardless of the presenting symptom(s).

There is evidence that response to high-dose parenteral B-complex vitamins varies with the presenting condition e.g. ophthalmoplegia responding more rapidly than confusion (Thomson *et al.*, 1983; Harper *et al.*, 1986; Victor *et al.*, 1989). A noticeable improvement in delirium/acute confusion is, however, said to occur in the majority of cases within 1–2 days (Wood and Currie, 1995). In some cases, repletion of other vitamins (e.g. folate/B_{12}) may also be necessary before a clinical response is achieved (Cole *et al.*, 1969).

Safety profile of parenteral B vitamin supplements

In January 1989 the UK Committee on Safety of Medicines (CSM) warned of the risk of serious allergic reactions that may occur during, or shortly after, the administration of Parentrovite (Committee on Safety of Medicines, 1989) — the thiamine component being thought to be responsible for these reactions (Wrenn and Slovis, 1992). Between 1970 and 1988, the Committee received 90 reports of adverse reactions associated with Parentrovite (72 associated with i.v. administration and 18 with the i.m. preparation). The most frequently reported reactions were anaphylaxis (41 cases), dyspnoea/bronchospasm (13 cases), rash/flushing (22 cases). The proportion of anaphylactic and serious allergic reactions is reported to be significantly greater for the i.v. route than for the i.m. route (58 vs 3, respectively $P < 0.001$) (O'Brien, 1995). To put this into context, between 0.5–1 million pairs of ampoules of each preparation of Parentrovite were sold annually in the UK in the 19 years that the CSM *Current Problems* adverse event data were collected. There were thus approximately four reports of an anaphylactoid reaction for every 1 million pairs of i.v. ampoules sold and one report per 5 million pairs of i.m.

ampoules sold. It would appear, therefore, that serious allergic reactions are very infrequent and significantly less likely to occur with the i.m. presentation.

Two retrospective studies on the safety of parenteral thiamine (which is used, exclusively, in the US) provide similar findings (Wrenn *et al.*, 1989; Wrenn and Slovis, 1992). The authors found one case of generalized pruritis in 989 patients, receiving a total of 1070 doses of thiamine (Wrenn *et al.*, 1989) and no significant allergic reactions in more than 300 000 patients treated with parenteral thiamine (Wrenn and Slovis, 1992). As Wrenn stated, 'This compares to a 1% to 10% chance of allergic reaction to penicillin, a 2% to 3% chance of a contrast media reaction, and a 1% to 18% chance of an allergic response to streptokinase' (Wrenn and Slovis, 1992).

Current management in the UK

The utilization of parenteral B-complex vitamins has altered markedly in the UK over the past 10 years. It is not entirely clear why this may have occurred, although two possible contributory factors may be identified: (1) parentrovite i.v. and i.m. presentations were withdrawn, and discontinued worldwide, in November 1992 (due to manufacturing problems). After a 9-month interval an identical i.v. preparation, Pabrinex i.v., was introduced. After another 10 months, an identical i.m. preparation, Pabrinex i.m., was also made available. (2) In 1989, a Committee on the Safety of Medicines *Current Problems* warning was issued relating to Parentrovite and allergic reactions (Committee on Safety of Medicines, 1989).

In September 1994, a survey was conducted on methods of thiamine replacement used for alcoholics in hospitals in England and Wales (D. Taylor and J. Marshall; personal communication). Questionnaires were sent to 273 hospital chief pharmacists who were asked to state the most commonly used thiamine replacement regimen for four indications: alcohol misusers admitted for observation (e.g. detoxification); alcohol misusers with suspected severe vitamin deficiency; those with suspected Wernicke's encephalopathy; and those with confirmed Wernicke's encephalopathy. The findings showed a shift towards increased use of oral supplements, and decreased use of parenteral supplements, for all indications, even for suspected and confirmed cases of Wernicke's encephalopathy.

A similar decline in the use of parenteral thiamine/B-complex vitamins in 'at-risk' alcoholics has also recently been documented by those working with patients who have sustained head injury (Ferguson *et al.*, 1996). Survivors of traumatic brain injury commonly suffer from a combination of cognitive and physical disabilities. Alcohol is a significant factor in head injury, influencing severity and frequency of injury, as well as affecting course and outcome following injury (Glucksman, 1994; Dikman *et al.*, 1995). One out of every two patients who sustain a head injury is likely to have an alcohol problem (compared with only about one in 10 in the general population) and an alcoholic's risk of subsequent head injury doubles with each injury (Dikman *et al.*, 1995).

In a 2-year survey (1993–1995) of traumatic head injury admissions in Edinburgh, Ferguson *et al.* (1996) found that, of 218 patients with a history of alcohol consumption prior to their accidents, only 11 received parenteral B-complex vitamins. In the 83 patients classified as alcoholic ($n = 41$) or heavy/harmful drinkers ($n = 42$), only eight (9.6%) received parenteral B-complex vitamins and all but one received suboptimal therapy.

As can be seen in Fig. 1, the decline in sales of parenteral high-potency B-complex vitamins predated the CSM adverse reaction warning, and therefore may have reflected a more general awareness of reported adverse reactions, or else may have been due to other unknown factors. Following the 9–10-month gap during which parenteral high-potency B-complex vitamins were not available in the UK, sales recommenced at a level well below that which had existed prior to the discontinuation of Parentrovite. The interruption of availability therefore appears to have been a particularly significant factor affecting the usage of high-potency B-complex vitamins. However, the perceived significance of the discontinuation of Parentrovite may have been affected by the prior publication of the CSM warning, and it may be that it was the combination of both factors which led to the failure of sales to recover after the reintroduction of a parenteral B-complex vitamin preparation in the form of Pabrinex.

As discussed, over the 6-year period for which data are available, there has been a 65% increase in reported admissions for cases of alcoholic

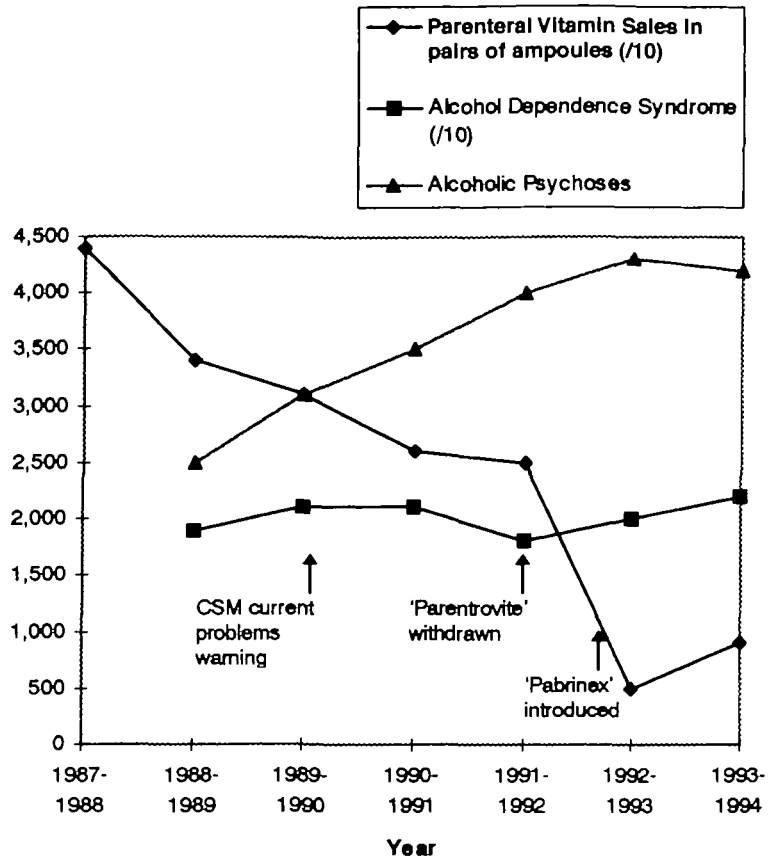

Fig. 1. Admissions for alcoholic psychoses (ICD-9 code 291) and alcohol-dependence syndrome (ICD-9 code 303), in National Health Service hospitals and sales of parenteral B-complex vitamins in England 1988–1989 to 1993–1994. Source: Hospital Episode Statistics, Department of Health and sales data from IMS/Link. Note: Hospital Episode Statistics are not available for the period prior to 1988–1989. A change in ICD-9 and ICD-10 revisions for 1994–1995 and ensuing major differences in coding definitions mean that data from 1994 onwards cannot be compared to previous data.

psychoses (ICD-9 code 291) and this is significantly inversely correlated with the declining sales of parenteral B-complex vitamins ($r = -0.846$, 95% confidence interval −0.983 to 0.431; $P = 0.034$). The proportion of 'alcoholic psychoses' contributed by patients with WKS is unknown. However, as discussed previously, WKS cannot be easily diagnosed and may be confused with delirium tremens (ICD-9 Code 291.0). It therefore appears that the CSM recommendations have been misinterpreted by psychiatrists in the UK, and that they have led to a change to the use of oral thiamine supplements, in preference to parenteral supplements, even where that is inappropriate due to malnutrition or heavy recent alcohol intake (O'Brien, 1995).

GENERAL CONCLUSIONS AND RECOMMENDATIONS

B vitamin deficiencies are common in alcohol misuse and dependence. WKS is also a common condition, associated with significant morbidity and mortality. Despite this, current practice in the UK commonly appears to be inadequate when viewed in the light of the published research evidence. There is therefore clearly a need to educate medical staff, and to establish agreed

guidelines for good practice.

It is clear that oral thiamine supplementation is inadequate and ineffective. Parenteral supplements are associated with an extremely low incidence of serious adverse effects. Therefore, both prophylaxis and treatment should be routinely based upon parenteral vitamin supplementation. However, in recognition of the small risk of anaphylactic reactions, and in accordance with the CSM guidance, administration of these supplements should only take place when appropriate resuscitation facilities (including trained staff as well as drugs and equipment) are immediately available.

Where the i.v. route of administration is used, the high-potency vitamins should be given by intermittent infusion wherever possible. The contents of the pairs of ampoules should be diluted with 50–100 ml of normal saline or 5% (w/v) dextrose and infused over a 15–30 min period. Dilution is thought to reduce the speed of onset and severity of any allergic reactions, if they should occur.

Given the high prevalence of B vitamin deficiency in alcohol-dependent patients, the increased thiamine requirement associated with the increased metabolic demands at alcohol withdrawal, and the lack of rapid efficient laboratory tests for B vitamin deficiency, it would appear to be wise to provide prophylactic B vitamin supplementation for all patients who undergo alcohol withdrawal on an in-patient basis. We would suggest that this should include patients admitted for other reasons who are subsequently found to experience moderate to severe alcohol withdrawal. We would recommend that the prophylactic dose should be a minimum of one pair of ampoules of i.m. (or i.v.) high potency vitamins B and C, given once daily for the first 3 to 5 days of in-patient alcohol detoxification.

Given the difficulties in diagnosis of WKS, there should be a low threshold for making a presumptive diagnosis, based upon broad criteria. We would argue that patients who develop any one or more of the following symptoms, in the context of a known or suspected history of alcohol misuse, should be assigned a presumptive diagnosis of Wernicke's encephalopathy: ophthalmoplegia; ataxia; acute confusion; memory disturbance; coma/unconsciousness; hypothermia and hypotension.

There is a particular danger of the diagnosis being missed in the case of patients admitted with a head injury. The history of alcohol misuse may not be available, and the signs and symptoms of Wernicke's encephalopathy may be attributed to the head injury. If there is any doubt about the possibility of alcohol dependence, a prophylactic regimen of B vitamin supplementation should be prescribed (as earlier). If there is any doubt about a possible diagnosis of Wernicke's encephalopathy, then a presumptive diagnosis should be made and treatment instituted accordingly.

Any patient with a presumptive diagnosis of WKS should then receive an appropriate therapeutic regimen of B vitamin supplementation. We would recommend a minimum of two pairs of i.v. high-potency B-complex vitamins three times daily for 2 consecutive days. If no response to therapy is observed after this time period (unless the patient is comatose/unconscious or the diagnosis of Wernicke's encephalopathy is confirmed by other means), treatment should be discontinued. If an objective response is observed, treatment should be continued for a further 5 days with one pair of i.v. or i.m. high-potency vitamins given once daily. However, for patients with enduring ataxia, polyneuritis or memory disturbance, high-potency vitamins should be given for as long as improvement continues (Guthrie and Elliot, 1980; Lishman, 1987*b*).

In community-based detoxification programmes, the therapeutic options are: (1) no vitamin supplementation; (2) oral B complex vitamin supplementation (with the attendant probability of poor absorption and possibly also poor compliance); (3) attendance of the patient at a hospital or clinic for administration of parenteral B-complex vitamins in a supervised setting (with appropriate resuscitation facilities available). In at-risk alcoholics unwilling or unable to be admitted for detoxification, the third option would particularly warrant serious consideration.

In conclusion, there appears therefore to be a current climate of under-recognition and poor clinical management of WKS in the UK. This condition is both common and associated with high morbidity and mortality. Parenteral vitamin supplementation provides a safe and effective form of prophylaxis and treatment. In-patients undergoing hospital-based detoxification and patients with a presumptive diagnosis of WKS

should be treated promptly with high-potency parenteral B-complex vitamins.

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