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Systematic review of nutritional interventions for people admitted to hospital for alcohol withdrawal

Cameron McLean

University of Wollongong, cjm853@uowmail.edu.au

Linda C. Tapsell

University of Wollongong, ltapsell@uow.edu.au

Sara J. Grafenauer

University of Wollongong, sarag@uow.edu.au

Anne T. McMahon

University of Wollongong, amcmahon@uow.edu.au

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A systematic review of nutritional interventions for people admitted to hospital for alcohol withdrawal

Authors

Cameron McLean, Msc. APD Clinical Dietitian and PhD Candidate

Nutrition and Dietetics Department, St George Hospital, Kogarah, NSW, Australia

Nutrition and Dietetics, School of Medicine, University of Wollongong, Wollongong, NSW, Australia

Linda Tapsell, PhD, FDAA, Senior Professor

Nutrition and Dietetics, School of Medicine, University of Wollongong, Wollongong, NSW, Australia

Sara Grafenauer, PhD, AdvAPD, Honorary Fellow

Nutrition and Dietetics, School of Medicine, University of Wollongong, Wollongong, NSW, Australia

Anne-Therese McMahon, PhD, APD, Senior Lecturer

Public Health Nutrition, School of Health and Society, University of Wollongong, Wollongong, NSW, Australia

Authorship

CM wrote the article. CM, ATM, SG and LT contributed to conception and design of this research. CM developed and complete the search strategy, screening and descriptive analysis of results under the direct supervision of ATM, SG and LT. All authors agree with the manuscript and declare that the content has not been published elsewhere.

Author Correspondence

Cameron McLean

Address: Nutrition and Dietetics Department, St George Hospital, Kogarah, NSW, Australia

Email: cameron.mclean@health.nsw.gov.au

Phone no: (02) 9113 2752

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interventions. Future research might also consider total dietary interventions as well as studies on the perspectives of people undergoing alcohol withdrawal.

Keywords: alcohol related disorders, alcoholism, malnutrition, nutrition therapy, thiamine, outcome assessment (health care)

Introduction

Alcohol consumption is driven by a number of internal and external influences that can be either positive or negative, for reasons such as a behavioural control, emotional coping strategies, socially for pleasure or enjoyment, historically for medicinal purposes, cultural practice, religious rituals, and sometimes for the purpose of intoxication.¹⁻³ There is ongoing debate within the scientific literature that the moderate consumption of alcohol may provide some health benefits.⁴⁻⁵ However, this position should be interpreted with caution. A previous meta-analysis has highlighted that there is no benefit of moderate alcohol consumption on mortality outcomes in a healthy population.⁶ A systematic analysis of the data from the Global Burden of Disease study has highlighted alcohol consumption as the seventh leading risk factor for premature death and disability internationally in 2016.⁷ Although there are guidelines available in at least 37 countries to reduce the health risks from consuming alcohol,⁸ this most recent systematic analysis suggests that there may be no safe level of alcohol consumption that minimises the negative effects of alcohol use.⁷

Alcohol Use Disorder (AUD) is a diagnosis characterised by an increased tolerance to the effects of alcohol consumption, impaired control over the consumption of alcohol, a presence of psychological and physiological harms or withdrawal signs and symptoms.⁹ Individuals with a diagnosis of an AUD experience significantly increased rates of mortality across the lifespan.¹⁰⁻¹²

Chronic alcohol consumption or intoxication is known to inhibit various neurotransmitter systems.¹³ The onset and severity of these signs and symptoms is influenced by a number of factors.¹³⁻¹⁴ There are a range of signs and symptoms associated with alcohol withdrawal from less severe such as tremulousness to more severe such as confusion and auditory or visual hallucinations.¹³⁻¹⁴ Some of these symptoms may be associated with a nutritional deficiency. The chronic consumption of alcohol is known to contribute to micronutrient deficiency, in

particular thiamine deficiency.¹⁵⁻¹⁶ Wernicke's Encephalopathy (WE) is an acute neurological condition associated with thiamine deficiency, that if left untreated can lead to irreversible brain damage known as Korsakoff Syndrome.¹⁵⁻¹⁶ Thus first line nutrition interventions for AUD often involve thiamine supplementation.

A more comprehensive approach to nutritional intervention in this patient group may emerge from a global assessment of malnutrition.²⁶⁻²⁸ Patients undergoing drug and alcohol treatment are frequently identified as being malnourished due to multiple serum micronutrient insufficiencies and altered body composition. These micronutrient insufficiencies have been shown to improve with nutrition interventions.¹⁷⁻¹⁹ It is difficult to compare the rates of malnutrition across studies given the variance in assessment tools used and the difficulty in obtaining an accurate history from these patients who may be cognitively impaired.²⁰ Consequently, the prevalence of malnutrition is likely to underestimate the number of nutritional risk factors and the severity of micronutrient deficiency in this population.¹⁸ A clinical examination may be more sensitive than biomarkers to determine rates of malnutrition in patients with an AUD.²¹ In a cohort of patients admitted to hospital for inpatient withdrawal from alcohol, 53% of patients were identified at medium or high risk of malnutrition despite having a normal Body Mass Index (BMI).²² Nutrient deficiencies in this patient population result from reduced dietary intake of nutrient dense food compounded by the effects of chronic alcohol consumption impairing nutrient digestion, absorption, metabolism and utilisation.¹⁸⁻¹⁹ Thus nutritional interventions beyond thiamine supplementation are called for.

A hospital admission may be required for severe cases of alcohol withdrawal for medical management and symptom control to prevent the development of severe complications such as seizures or delirium tremens which if left untreated may result in death.¹³⁻¹⁴ Those most likely to be admitted to hospital for the management of alcohol withdrawal are patients presenting

with severe withdrawal symptoms, a history of severe alcohol withdrawal symptoms, psychiatric or concurrent medical disorders which may complicate management.²³⁻²⁴ The purpose of alcohol withdrawal management is to interrupt the pattern of heavy and regular alcohol use; alleviate withdrawal symptoms; prevent severe withdrawal complications; facilitate links to ongoing treatment; and provide assistance with other co-occurring conditions (such as access to accommodation, food and speciality medical management including mental health services).²³⁻

²⁴ Interventions relating to these issues could cover a range of problematic areas and include nutritional interventions and lifestyle education programs.

Given the above, the aim of this review is to describe the nature of nutritional interventions for people admitted to hospital for alcohol withdrawal reported in the scientific literature and to report on the health outcomes achieved.

Methods

This systematic literature review followed the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).²⁵ This review was registered with the International Prospective Register Of Systematic Reviews (PROSPERO) (<http://www.crd.york.ac.uk/PROSPERO>; registration number: CRD42017081884).

A systematic search of the databases CINAHL, MEDLINE, PsycARTICLES, PsycINFO, Scopus and Web of Science was conducted in April 2018. Initially, a scoping review was carried out of these databases to identify all relevant key terms for inclusion. As recommended by Rosen and colleagues free text terms were used in combination with Medical Subject Headings (MESH) for MEDLINE and CINAHL databases.²⁶ The two (2) following search strategies were applied: (1) 'alcoholism OR alcohol related disorder OR alcohol depen* OR alcohol* intoxi* OR AUD OR alcohol use disorder OR alcohol disorder' AND 'nutri* OR diet* OR vitamin OR mineral OR diet* supplement* OR nutri* supplement* OR nutri* educat* OR diet* educat*'; and (2) MESH

headings applied to MEDLINE and CINAHL databases 'nutri* OR diet* OR vitamin OR mineral OR diet* supplement* OR nutri* supplement* OR nutri* educat* OR diet* educat*' AND MESH Alcoholism OR Alcohol Related Disorders. The reference lists of eligible articles and relevant reviews were also screened for potential publications for inclusion. The search was repeated in November 2018 and no new eligible papers were identified.

To be included in this review studies were required to meet the following inclusion criteria: (1) prospective studies conducted in humans aged 18 years and above; (2) studies available in the English language; (3) hospital inpatient based setting; and (4) primary reason for admission to hospital as alcohol withdrawal. The following exclusion criteria was applied: (1) populations with a diagnosis of liver cirrhosis; (2) populations with a diagnosis of pancreatitis; and (3) case reports or case studies. There was no restriction placed on journal article publication date.

There were a large number of different interventions ranging from single nutrient supplementation such as thiamine through to those that were educational based. The outcomes reported on ranged from biochemical based through to symptoms of alcohol withdrawal.

Articles were screened based on title and abstract. In the absence of an abstract or sufficient information to draw a conclusion regarding inclusion within the review, the full text was retrieved. Abstract screening was completed by CM under supervision where considerations of uncertainty resolved via consensus with ATM, SG and LT.

The following data were extracted: citation, country, sample size, setting, study design, nutrition intervention and duration, outcome measures, and details of control group (if applicable). A descriptive summary is provided.

The Quality Criteria Checklist for Primary Research produced by The Academy of Nutrition and Dietetics was used to assess the research design.²⁷ The Quality Criteria Checklist includes four

relevance questions around applicability to practice and ten validity questions that address scientific soundness of the research. The article is designated either a negative (-), neutral (0) or positive rating (+).

Results

Following removal of duplicates a total of 11, 922 articles were identified from the systematic search. After applying the exclusion criteria 11, 803 articles were removed leaving 119 full text articles. After assessment for eligibility, 14 studies were included in the descriptive synthesis. The process is displayed in the PRISMA diagram (Figure 1).

Most of the 14 studies were conducted in the USA,²⁸⁻³¹ followed by the UK,³²⁻³⁴ and then Croatia,³⁵ Poland,³⁶ France,¹⁷ Russia,³⁷ Canada,³⁸ Australia,³⁹ and Sweden.⁴⁰ Intervention periods ranged from 1 day to 40 days. Studies were published between 1968 and 2013 but only 4 (28%) in the last 10 years. Sample sizes ranged from 16 to 236 participants, with an age range of 38 to 50 years. Male participants comprised from 20 to 100 % of the various samples. The quality of research design of papers included in this review was largely positive. These characteristics are displayed in Table 2.

All but one of the studies focused on single nutrients – supplementation occurred with various forms of vitamins and minerals or compounds with anti-oxidant activity (which may include vitamins) or probiotics. Only one study was an educational intervention. There were no studies investigating comprehensive dietary interventions targeting overall amelioration of symptoms and the recovery of supportive eating habits.

There were a number of studies looking at single nutrient supplementation. There were two studies that reviewed the effects of thiamine supplementation, on functional and metabolic outcomes respectively.³⁹⁻⁴⁰ One of these used daily intramuscular thiamine hydrochloride at different dosages (5, 20, 100 or 200 mg) to show a dose related effect on working memory

performance measured by a delayed alternation task.³⁹ The other investigated the effects of oral thiamine (50 mg) compared to a standard hospital diet (containing 0.8 – 1.5 mg thiamine) on serum thiamine and transketolase activity.⁴⁰ The thiamine di-phosphate (TDP) effect reflects the extent of unsaturation of transketolase with TDP.⁴¹ This study demonstrated that orally delivered thiamine shifted the TDP effect towards normal, whereas the thiamine content of the hospital diet alone was insufficient.⁴¹ There was one study that investigated the effects of intramuscular magnesium sulphate on severity of alcohol withdrawal symptoms and serum magnesium levels compared to placebo, demonstrating no statistically significant differences between groups.³⁸

Two studies investigated the effects of amino-acids delivered through supplements or food sources respectively on different stress parameters.^{31,35} The first investigated the effects of an amino acid supplement on restoration of brain neurotransmitter balance in both alcohol dependent and poly-drug users.³¹ There was a significant improvement in stress response, physical response to alcohol withdrawal, behavioral and emotional wellbeing by day 7 of withdrawal in those who were alcohol dependent.³¹ The second study investigated the effects of a food based supplement on alcohol withdrawal symptoms demonstrating a significant decline in all psychiatric symptoms (except anxiety) compared to day one of admission within the intervention group.³⁵

Three studies investigated the effects of various forms of 'antioxidant' supplements.^{17,32,36} The first demonstrated no significant effect on free radical activity as measured by diene conjugated linoleic acid assay, but in the supplemented group (containing vitamin E, C, selenium and beta-carotene) serum levels of vitamin E and beta-carotene improved.³² The next showed that compared to placebo, the supplemented group (containing vitamin C, beta-carotene, alpha-tocopherol, zinc and selenium) had increased serum levels of vitamin C, alpha-tocopherol, beta-

carotene, zinc and selenium after 21 days.¹⁷ The third study investigated the effects of capsules of borage oil enriched with vitamin E on lysosomal exoglycosidases. Increased levels of exoglycosidases in serum has been shown as an indication of inflammatory disease and alcoholism.³⁶ At the completion of the study, there were no significant differences between groups.³⁶

Two studies investigated the effects of multivitamin supplementation.³³⁻³⁴ The first compared the effects of oral (5 tablets daily each containing 50 mg thiamine) and intramuscular multivitamin supplement (one injection daily containing 250 mg thiamine) compared to no supplement on erythrocyte levels of thiamine diphosphate (ETDP).³⁴ The results demonstrated that the parenteral route more rapidly raised serum levels of ETDP, however oral supplementation was as efficacious in producing mean increases in serum ETDP levels by day 5.³⁴ The second study investigated the effects of oral and intravenous multivitamin supplementation (containing thiamine, riboflavin, pyridoxine, nicotinamide and ascorbic acid) compared to no supplementation at all.³³ Thiamine, riboflavin and pyridoxine status were assessed by measurement of erythrocyte transketolase (ETK), glutathione reductase (EGR) and glutamate oxaloacetate transaminase (EGOT) respectively.³³ By day 5 of the intervention there were improvements seen in all participants in terms of enzyme activity, regardless of the intervention.³³ Of those who were thiamine deficient at baseline (47/73), most remained deficient regardless of the intervention (31/73).³³ However, depending on the method of assessment used to assess thiamine deficiency, when assessed by the activation coefficient for transketolase fewer participants (10/73) were identified as deficient by day 5.³³

Two studies investigated the effects of oral liquid nutrition supplementation.^{28,30} The first study investigated the effects of a protein supplement (containing 1200 kJ and 48 g protein) on weight change, liver enzyme activity (serum glutamic oxaloacetic transaminase (SGOT), mental

attitude and sedation requirement during alcohol withdrawal.²⁸ Although a causal relationship was not demonstrated with oral nutrition support, there were observed increases in body weight.²⁸ The second study evaluated the effects of an oral fructose based supplement (containing 50 g fructose) on symptoms of alcohol withdrawal syndrome.³⁰ The fructose based supplement did not demonstrate a more rapid alleviation of withdrawal symptoms when compared to control.³⁰

Only one study investigated the effects of a probiotic supplement (containing *B. bifidum* and *L. Plantarum* bacteria) on bowel flora.³⁷ In the intervention group there were significant increases in levels of bifidobacteria, enterococci and lactobacilli similar to those seen in healthy controls at day 5.³⁷ Furthermore, when compared to the control at the end of treatment the probiotic group had significantly lower liver function tests, reflective of reduced alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.³⁷

Only one study investigated the effects of an educational intervention on knowledge outcomes. There was no significant improvement observed in basic nutrition, digestion, absorption and metabolism knowledge.²⁹ However, the intervention group scored significantly higher in areas of consumer practices (i.e. information around health foods, synthetic and natural vitamin sources and economics factors influencing purchase), alcohol and nutrition and their overall test scores.²⁹

Discussion

The current review identified 14 studies investigating the effects of nutritional based interventions on health-related outcomes in patients admitted to hospital for alcohol withdrawal. A broad range of interventions, largely involving single nutrients, were identified ranging from supplementation with thiamine, amino acids, antioxidants, probiotics and magnesium to educational intervention. Current inpatient guidelines for alcohol withdrawal

focus on supportive care across the admission, from a nutritional perspective this includes encouraging oral intake, the provision of supplements (including thiamine), ensuring adequate hydration and the monitoring of nutritional status.²³⁻²⁴ Although not routinely indicated, patients may benefit from baseline pathology assessment such as serum electrolytes, calcium, magnesium, iron and vitamin levels for those who may have poor dietary intake or may be at risk of refeeding syndrome.⁴² Electrolyte disturbances are common in patients who chronically consume alcohol,⁴³ however the incidence of refeeding syndrome is low.⁴⁴ A dietitian can assist in determining risk of refeeding syndrome and provide input on appropriate management, whilst providing holistic and targeted advice supporting food based dietary patterns and supplement recommendations that incorporate psychosocial aspects which can lead to long term sustainable health outcomes.

Pre-existing literature and international guidelines on alcohol withdrawal management highlight the importance of thiamine in the treatment and prevention of WE.^{2,23-24,45-46} Currently, evidence from randomised controlled trials is insufficient to guide dose, frequency and route of administration against or for the treatment of WE.⁴⁶ This current review reported on a number of studies investigating the effects of thiamine alone,³⁹⁻⁴⁰ or included in a multivitamin formulation.³³⁻³⁴ Although the studies reported here have reported similar improvements in serum thiamine and enzyme activity levels when comparing oral or parenteral thiamine administration,^{33-34,40} these studies may be of inadequate duration to demonstrate a central nervous system response.⁴⁰ International guidelines recommend parenteral thiamine for people with suspected WE, or those who may show signs of malnourishment over 3 to 5 days.^{2,23-24,45-46} In these guidelines, thiamine dosages of up to a minimum of 500 mg are recommended for patients suspected of WE,^{23-24,45} and this is considered to be a safe and effective form of treatment.⁴⁵ Despite the introduction of mandatory and voluntary fortification with thiamine in staple grain foods such as bread in both developing and developed countries,⁴⁷ the studies

reported on in this review did not review participant dietary patterns to identify food based thiamine intake prior to supplementation. Oral thiamine supplementation may still remain important for those with alcohol dependence following inpatient alcohol withdrawal,⁴⁸ from a nutrient adequacy and utilisation perspective.

Patients with an AUD display a range of neurocognitive deficits and inhibitory control.^{20, 49} Cognitive impairments are likely to impact on the efficacy of management and compromise treatment outcomes in those with an AUD.⁴⁹ Although abstinence is associated with cognitive recovery, some residual deficits may interfere with effective treatment.^{20,49} In this review only one study investigated the improvement of knowledge after a nutrition education session.²⁹ However, this study only evaluated the immediate improvement of knowledge post intervention and the retention of this knowledge was not evaluated. Previous research surrounding the individualised nutritional care post alcohol withdrawal has reflected improved micronutrient intake and lower alcohol intake at four month follow up when compared to control groups.⁵⁰ Substance abuse treatment programs offering a holistic treatment approach, including group nutrition education have been associated with positive treatment outcomes, thus supporting nutritional education as an essential component of alcohol treatment programs.⁵¹ Consideration should be made surrounding cognitive function and ability to provide accurate information as well as retain information when providing nutritional counselling to patients with an AUD.

There were no identified studies included in this review that focussed on addressing malnutrition despite the known nutritional risk of this patient population. A recent systematic literature review undertook a review of interventions for the prevention or treatment of malnutrition in homeless problem drinkers.⁵² Although participants were not recruited from a hospital inpatient admission for alcohol withdrawal, the outcomes reported in this review are

relevant when considering nutritional intervention on discharge from acute hospital based care. Interventions included education, supplementation (i.e. intramuscular, oral tablet or fortified food product based), and provision of food products (i.e. hot meals or food rations). Although multicomponent interventions lead to improved nutritional behaviour in some studies, results were not consistent across others.⁵² Therefore, holistic and individualised nutritional interventions post admission to hospital should be formulated by a trained nutritional professional, considering psychosocial aspects of care and long term follow up and evaluation. This may include the involvement of other allied health professionals, to ensure treatment effectiveness.

The hospital length of stay is likely to influence the efficacy of treatment and health outcomes. The length of nutrition intervention in this study ranged from one day to forty days. Addiction, in the context of an AUD, should be considered a chronic health condition.⁵³ Whereby the continual engagement and individualised treatment services on discharge is likely to lead to successful long-term treatment outcomes.⁵⁴ However, the hospital admission provides the opportunity to engage with patients and to co-ordinate post discharge care.²³⁻²⁵ The continuation of nutritional intervention, monitoring and support on discharge from acute care is likely to contribute to improved nutrition related outcomes in this patient population and should be further evaluated.

Holistic management inclusive of malnutrition screening seems to be most appropriate for this group of patients identified at nutritional risk. The literature provides some promising insights into nutritional approaches that address health outcomes, however a more comprehensive approach that addresses the overall amelioration of symptoms and the restoration of supportive eating habits across all stages of an Alcohol Use Disorder is required. Future research

would be further supported by considering the perspectives of people undergoing alcohol withdrawal to contribute to more meaningful recommendations for practice.

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Figure 1: PRISMA diagram.

Citation Country	Sample size (N), mean age (years) proportion males (%)	Study Design	Intervention	Outcome Measures	Quality Criteria Checklist Rating (-, 0, +)	Results
Ambrose 2001 Australia	N= 107, 47 years, not disclosed	A (randomised controlled trial)	Intramuscular thiamine hydrochloride once daily as: 5, 20, 50, 100 or 200 mg Duration: 2 days	Delayed alteration task Note: criterion defined as 12 consecutive correct responses	+	Fewer trials to reach criterion in 200 mg intervention compared between groups ($p=0.047$) a and mean of other dosage groups ($p=0.031$) ^b
Waldenlind 1981 Sweden	N= 41, 43 years, 75% male	C (non- randomised- controlled trial)	Treatment: 50mg thiamine daily orally Comparator: standard hospital diet only (0.8-1.5mg thiamine/day) Duration: 10 days (final measures taken 2 days after last dose)	Serum thiamine Transketolase Thiamine diphosphate (TDP) effect	+	Increase in serum thiamine levels in treatment group ($p<0.02$) ^b Increase transketolase activity in treatment group ($p<0.10$) ^b

						TDP effect restored towards normal in treatment group (NS) ^b
Wilson 1984 Canada	N= 100, 45 years, 79% male	A (randomised controlled trial)	<p>Treatment: magnesium sulphate 2 g every 6 hours intramuscularly (four injections in a total of 24-hour period)</p> <p>Control: 0.9 % sodium chloride solution (four injections in a total of 24-hour period)</p> <p>Duration: 1 day (24 hours)</p>	<p>Serum magnesium</p> <p>Severity of alcohol withdrawal seven point scale (diaphoresis, tremor, vomiting, hallucination, and overall test score)</p> <p>Amount of chlordiazepoxide</p>	+	<p>Effect of treatment on alcohol withdrawal symptoms (NS)^b</p> <p>Higher serum magnesium levels at 24-hours and 48-hours in treatment group ($p<0.05$)^b</p> <p>Sedative requirement between groups ($p>0.10$)^b</p>
Blum 1989 United States of America	N=25, 38 years, 80% male	A (randomised controlled trial)	Treatment: 2 SAAVE capsules containing D-phenylalanine 230mg, L-phenylalanine 230mg, L-tryptophan 25mg, L-glutamine 25mg, Pyridoxal 5'-phosphate 5mg three times	Skin conductance level (SCL)	0	Lower SCL at day 7 in the treatment group ($p<0.025$) ^a , treatment group remains lower at

			<p>daily</p> <p>Control: placebo capsules (methyl cellulose)</p> <p>Duration: 21 days (and 7 days follow up)</p>	<p>Behavioural Spiritual and Social (BESS) score</p> <p>Physical Score (PS)</p>		<p>other time points (NS)</p> <p>Lower PS in treatment group at day 7 ($p<0.004$)^b higher levels at day 21 and 28 (NS)</p> <p>Greater improvement in BESS score in treatment group at day 10, 21 and 28 ($p<0.001$)^b</p>
Jukic 2011 Croatia	N=20, 42 year, 75% male	A (randomised controlled trial)	<p>Treatment: one capsule daily (300mg d/l-phenylalanine, 150mg l-glutamine, 5mg l-5-hidroksitriptofane, 1mg vitamin B6, 50mg calcium gluconate, 25mg magnesium oxide, 0.01mg folic acid).</p> <p>Control: capsule (1mg of vitamin B6, 50mg calcium</p>	<p>Serum cortisol</p> <p>Psychological testing SCL-90-R</p> <p>Note: SCL-90 R measures of somatization, obsessive compulsive, interpersonal</p>	+	<p>Decline in serum cortisol at day 40 of admission in both groups ($p<0.05$)^b, NS between groups</p> <p>Fewer psychiatric symptoms in treatment group at day 40 of admission</p>

			gluconate, 25mg magnesium oxide 0.01mg folic acid). Duration: 40 days	sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, global index of disturbance.		($p<0.05$) ^b , exception anxiety ($p=0.056$) ^b
Butcher 1993 United Kingdom	N=28, 45 years, 60 % male	C (non- randomised controlled trial)	Treatment: Antioxidant mixture containing: vitamin E 400mg, beta-carotene 40mg, vitamin C 1000mg, selenium 10ug Control: Placebo. Duration: 7 days.	Diene Conjugate of Linoleic Acid (DCLA) Serum vitamin E Serum Beta-Carotene Serum Aspartate Transaminase (AST)	+	Similar decrease in DCLA between groups ($p=0.32$) ^c Decreased AST activity between treatment ($p=0.41$) ^c Greater increase in serum beta carotene ($p=0.034$) ^c and vitamin E ($p=0.006$) ^c in treatment group
Guegen 2013 France	N= 106, 41 years , 51 % male	A (randomised controlled trial)	Treatment: Antioxidant capsule (120mg vitamin C, 6mg Beta- Carotene (1000 retinol equivalents), 30mg alpha-	Serum Vitamin C Retinol	+	Increase in the treatment group when compared to control levels of:

			<p>Tocopherol, 20mg Zinc and 100ug Selenium).</p> <p>Control: Placebo capsule (not disclosed)</p> <p>Duration: 21 days</p>	<p>Alpha-tocopherol</p> <p>Beta-cryptoxanthin</p> <p>Lycopene</p> <p>Alpha-carotene</p> <p>Beta-carotene</p> <p>Zinc</p> <p>Selenium</p>		<p>vitamin C ($p<0.001$)^b, alpha-tocopherol ($p<0.001$)^b, beta-carotene ($p<0.001$)^b, zinc ($p<0.01$)^b and selenium ($p<0.001$)^b</p> <p>Greater increase in lycopene in the control group compared to the treatment group ($p<0.05$)^b</p>
Zaniewska 2009 Poland	N= 16, 36 years, 100% male	C (non-randomised controlled trial)	<p>Treatment: borage oil enriched with vitamin E (Neoglandyna (72.5mg γ-linolenic acid, 129.5mg linoleic acid and 7.4mg vitamin E)) six capsules daily.</p> <p>Control: no supplementation (no placebo capsule).</p> <p>Duration: 30 days</p>	<p>Alpha-mannosidase (MAN)</p> <p>Alpha-fucosidase (FUC) Beta-glucuronidase (GLUCUR)</p>	+	<p>NS difference in MAN and GLUCUR activity^d</p> <p>Tendency for FUC activity to decrease in treatment group (NS)^d</p>

Baines 1988 United Kingdom	N=25, 39 years, 64 % male	A (randomised controlled trial)	<p>Treatment 1: Intramuscular multivitamin containing 250 mg thiamine once daily</p> <p>Treatment 2: Oral multivitamin supplement containing 50 mg thiamine five times daily</p> <p>Control: No supplementation at all</p> <p>Duration: 5 days</p>	Erythrocyte thiamine di-phosphate (ETDP) levels	0	After 5 days similar increase in mean ETDP levels, greater in the intramuscular group ($p<0.05$) ^b
Brown 1982 United Kingdom	N= 97, not disclosed, not disclosed	C (non-randomised controlled trial)	<p>Treatment 1: Intravenous Parentrovite HP (Bencard Ltd., Brentford, Middlesex, U.K.) 10mL 250mg thiamine HCL, 4mg riboflavin, 4mg pyridoxine, 160mg nicotinamide, 500mg ascorbic acid</p> <p>Treatment 2: 1 Orovite tablet (Bencard Ltd., Brentford, Middlesex, U.K.) Containing 150mg thiamine HCL, 15mg riboflavin, 15mg pyridoxine,</p>	<p>Erythrocyte Transketolase (ETK)</p> <p>Erythrocyte Glutathione Reductase (EGR)</p> <p>Erythrocyte glutamate oxalacetate transaminase (EGOT)</p> <p>Coefficient for enzyme activity also calculated</p>	+	<p>Increase ETK in intravenous and oral groups by day 2 ($p<0.05$)^b and all groups by day 5 ($p<0.001$)^b</p> <p>Improvement not demonstrated until day 5 when using alpha coefficient of ETK ($p<0.001$)^b</p>

			<p>600mg nicotinamide, 300mg ascorbic acid three times daily</p> <p>Control: placebo capsules one capsule three times daily (contents not disclosed)</p> <p>Duration: 5 days</p> <p>Note: all patients received 100 mg thiamine hydrochloride I.V. on admission (secondary to WE risk), interventions commenced thereafter.</p>			<p>Improvement in the activation coefficient EGR across all treatment groups demonstrated by day 2 ($p<0.05$, $p<0.05$ and $p<0.001$ respectively)^b. All groups improvement by day 5 ($p<0.001$)^b, however below normal ranges.</p> <p>Increase in alpha coefficient of EGOT in all groups demonstrated by day 2 ($p<0.001$)^b and day 5 ($p<0.001$, $p<0.01$ and $p<0.001$ respectively)^b</p>
Corley 1968 United States of America	N= 236, 45 years, 20 % male	C (non-randomised controlled trial)	Treatment: protein supplement (Provimalt, Fleet) twice daily (48g protein and 300 calories 2.1mg thiamine, 3.4mg riboflavin, 9.4mg niacin, 1500 USP vitamin A, 100 USP vitamin	Weight (increase or decrease) Tremor, Mental Attitude, Need for	-	A greater number of weight increases in the intervention group ($p<0.01$) ^b

			<p>D, 100mg ascorbic acid, 0.26mg pyridoxine, 3.4 ug cyanocobalamin, 1.7 mg pantothenic acid, 11.0 mg iron, 1100 mg calcium, 935 mg phosphorus, 0.85 mg copper, 0.17 mg magnesium, 380 mg sodium, 680 mg potassium and 850 mg chlorine).</p> <p>Control: following admission of patients over a two week period received no treatment.</p> <p>Duration: 5 days</p> <p>Note: every patient received one multivitamin capsule daily (Vigran Squibb) daily and 100 mg tablet of ascorbic acid.</p>	Sedative Medication (4-point scale)		Tremor, mental attitude or need for sedation (NS) ^b
Iber 1987 United States of America	N= 25, not disclosed, not disclosed	A (randomised controlled trial)	<p>Treatment: Oral Alcohol Treatment Supplement (OATS) Custom Laboratories, Inc of Baltimore) (50g fructose, 0g glucose, 50mg sodium, 50mg potassium, 40mg magnesium, 40mg calcium, 10mg zinc. Four</p>	<p>Serum potassium</p> <p>Serum zinc</p> <p>Serum magnesium</p> <p>Serum phosphorous</p>	+	No significant difference between treatment group and control group for all outcome measures ^b

			<p>(16oz) bottles in the first 24 hours followed by two on successive days.</p> <p>Control: placebo (50g glucose) four (16oz) bottles in the first 24 hours followed by two on successive days</p> <p>Duration: 3 days</p>	<p>Hand tremor</p> <p>Sleep score</p> <p>Ability to draw continuous line between two concentric circles</p> <p>Amount of sedative required</p> <p>Analogue scale of withdrawal symptoms (mental attitude, social participation, ability to relax, perceived hyperactivity and tremulousness)</p> <p>Analogue scale of representative behaviour (appetite, restlessness, blues, stomach and intestine unrest,</p>		
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				sufficiency of medication)		
Kirpich 2008 Russia	N= 66, 42 years, 100% male	A (randomised controlled trial)	<p>Treatment: Probiotic capsule (0.9 x 10⁸ Colony Forming Units (CFU) B. bifidum and 0.9 x 10⁹ CFU Lplantarum 8PA3)</p> <p>Control: Standard therapy (without probiotic supplement)</p> <p>Duration: 5 days</p> <p>Note: all patients scheduled on standard vitamin B1 and vitamin B 6 therapy (dosage not disclosed)</p>	<p>Aminotransferase (ALT)</p> <p>Aspartate aminotransferase (AST)</p> <p>Lactate dehydrogenase (LDH)</p> <p>Gamma glutamyl transpeptidase (GGT)</p> <p>Bilirubin</p> <p>Microbiological assay of bowel flora bifidobacteria, lactobacilli and enterococci from fecal samples.</p>	+	<p>Increased levels of bifidobacteria, enterococci and lactobacilli in the treatment group by day 5 (p<0.05)^b</p> <p>Lower ALT and AST in the treatment group by day 5 (p<0.05)^b</p>

Timmers 1988 United States of America	N=44, 34 years, 88% male	C (non-randomised controlled trial)	<p>Treatment: group education session via a slide show presentation and video materials on knowledge areas of basic nutrition; digestion, absorption and metabolism; consumer practices; alcohol and nutrition.</p> <p>Control: did not receive nutritional instruction alternative assignment based on admission to unit.</p> <p>Duration: 2.5 hours over 2 days</p>	Pre and post-test evaluation via 50 item questionnaire measuring knowledge based on key knowledge areas.	0	<p>Higher post-test scores in the treatment group in areas of consumerism ($p<0.001$)^b, alcohol and nutrition ($p<0.001$)^b and overall total test score ($p<0.001$)^b</p> <p>No significant improvements seen in areas of basic nutrition or digestion, absorption or metabolism</p>
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Footnote: a ANOVA b T-Test c Wilcoxon Rank Sum d Mann-Whitney U-Test

Quality Criteria Checklist Rating: Academy of Nutrition and Dietetics. Evidence analysis manual: steps in the Academy evidence analysis process. Chicago, IL 2016.

- 2 Table 1: characteristics of included studies of nutrition interventions and outcomes in patient admitted to hospital for alcohol withdrawal.