Vitamin B deficiencies and treatment

Vitamins are organic compounds that are essential for normal physiological functions and the maintenance of optimal health. They cannot be synthesised by the body and hence are required in small quantities in the diet. A deficiency thereof may cause specific nutritional medical disorders.[1,2]

Guidelines by the Merck Vitamin B Advisory Board

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The B-group (or B-complex) vitamins act as important co-enzymes in numerous metabolic processes and help the body convert carbohydrates into glucose for energy production, as well as to metabolise proteins and fats. B vitamins are also needed for the maintenance of healthy skin, hair, eyes, the liver and nervous system.[3-7] Some of the B vitamins are involved in the synthesis of red blood cells, neurotransmitters and nucleic acids such as RNA and DNA.[1,6,7] Refer to **Figure 1**. There are eight essential B vitamins that cannot be synthesised in the body and hence need to be ingested daily. Of these, deficiencies in the so-called BIG 5 (B_1, B_3, B_6, B_9, and B_{12}), can result in serious medically defined disorders.[2] See **Table 1**.

A well-balanced diet, including both plant and animal-based foods, will prevent the occurrence of Vitamin B deficiencies.[1] However, there are certain conditions that may predispose a person to the development of a vitamin B deficiency by either decreasing their intake or absorption of the B vitamins and/or increasing their need for or excretion of the B vitamins. Vitamin B deficiencies seldom occur in isolation.[1] Active supplementation of vitamins should generally only be used to correct documented deficiencies, after which a well-balanced diet should be resumed to provide all necessary nutrients.[1] Daily requirements of some of the B vitamins is listed in **Table 2**.

Table 2. Daily requirements of Vitamins B_1, B_2, B_3, B_6, B_9 and B_{12}[3-7]

Vitamin B	Daily requirements [3-7]		
	Adult males	Adult females	Pregnant females
B_1 (thiamine)	1,2mg	1,1mg	1,4mg
B_3 (niacin)	16mg	14mg	18mg
B_6 (pyridoxine)	1,3-1,7mg*	1,5mg	1,9mg
B_9 (folic acid)	400µg	400µg	600µg
B_{12} (cobalamin)	2,4µg	2,4µg	2,6µg

* 1,3mg up to age 50 years, 1,7 mg from 51 years

Conditions that predispose to vitamin B deficiencies

The elderly

In the elderly, pathophysiological changes, multiple comorbidities and increasing dependency can lead to malnutrition due to the inadequate intake and malabsorption of nutrients, vitamins and minerals.[9] See **Table 3**. B vitamin deficiencies, even subclinical deficiencies, in the elderly are important, as they have been linked to cognitive impairment, memory loss, depression, and dementia.[10-14]

Table 1. Vitamin B complex[1,8]

Vitamin B complex	Essential Vit B's	BIG 5	Deficiency
Vitamin B_1 (thiamine)	Thiamine	Thiamine	Beriberi, polyneuritis, Wernicke-Korsakoff syndrome
Vitamin B_2 (riboflavin)	Riboflavin		
Vitamin B_3 (niacin)	Niacin	Niacin	Pellagra (dermatitis, dementia, diarrhoea)
Vitamin B_5 (pantothenic acid)	Pantothenic acid		
Vitamin B_6 (pyridoxine)	Pyridoxine	Pyridoxine	Anaemia, dermatitis, depression, confusion, peripheral neuropathy
Vitamin B_7 (biotin)	Biotin		
Vitamin B_8 (inositol)			
Vitamin B_9 (folic acid)	Folic acid	Folic acid	Megaloblastic anaemia, neural tube defects
Vitamin B_{12} (cobalamin)	Cobalamin	Cobalamin	Megaloblastic anaemia, peripheral neuropathy
Para-aminobenzoic acid			
Choline			

Neurotropic B Vitamins (B_1, B_6 and B_{12}) are all necessary for healthy nerve function, and symptoms** of a Vitamin B deficiency may include: [1-4]

Forgetfulness, confusion


Mood disturbance


Pins-and-needles, numbness or weakness (hands & feet)


Difficulty walking, maintaining balance and ataxia

The elderly are at risk of Vitamin B deficiencies [5,6]

Pathophysiological changes, multiple comorbidities and increasing dependency can lead to malnutrition and vitamin deficiencies in the elderly [5]


Poor intake [5,6]


Poor absorption [5,6]


Increased requirements [7]


Increased excretion [8]

Other patients at risk of Vitamin B deficiency and/or neuropathy include: [9-11]


Vegetarians and vegans


Patients who consume excessive amounts of alcohol

Neurobion® - the market-leading Vitamin B complex product in 74 countries worldwide. ***[12]

** Symptoms may be related to another medical condition.

*** **Neurobion® is the market-leading Vitamin B complex product/ Vitamin B combination product for the last two-year period, based on a combined market of 74 countries worldwide.**

References: **1.** da Silva L, McCray S. Vitamin B_{12}: No One Should Be Without It. *Pract Gastroenterol* 2009:34-46. **2.** Disorders of Nutrition and Metabolism. Section 11. In: *The Merck Manual of Medical Information*. Second Edition. (eds) Beers SL, Bowman MA, Pocket Books, New York, London, Toronto, Sydney, Pp 918-926. **3.** National Institute of Health. Vitamin B_{12}. Dietary Supplement Fact Sheet. [online] [cited] 2017 Jan 17]. Available from: URL: http://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/. **4.** Frye RE, Griffing GT. Pyridoxine Deficiency Clinical Presentation. Medscape Reference: Drugs, Diseases and Procedures. [online] [cited 2017 Jan 2017]. Available from: URL: http://emedicine.medscape.com/article/124947-clinical. **5.** Wong CW. Vitamin B_{12} deficiency in the elderly: is it worth screening? *Hong Kong Med J* 2015;**21**:155-164. **6.** Andrès E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE, Noblet-Dick M, Maloisel F, Schlienger JL, Blicklé JF. Vitamin B_{12} (cobalamin) deficiency in elderly patients. *Canadian Medical Association Journal*. 2004;**171**(3):251-9. **7.** van der Wielen RPJ, Löwik MRH, Haller J, van den Berg H, Ferry M, van Staveren WA. Vitamin B_6 Malnutrition Among Elderly Europeans: The SENECA Study. *J Geront BIOL SCI* 1996;**51A**(6):B417-B424. **8.** Suter PM, Haller J, Hany A, Vetter W. Diuretic use: a risk for subclinical thiamine deficiency in elderly patients. *J Nutr Health Aging* 2000;**4**(2):69-71. **9.** Stabler SP. Vitamin B_{12} Deficiency. *N Eng J Med* 2013;**368**:149-160. **10.** Briani C, Torre CD, Citton V, Manara R, Pompanin S, Binotto G, Adami F. Cobalamin Deficiency: Clinical Picture and Radiological Findings. *Nutrients* 2013;**5**:4521-4539. **11.** Becker DA, Balcer LJ, Galetta SL. The Neurological Complications of Nutritional Deficiency following Bariatric Surgery. *J Obesity* 2012;2012. **12.** Internal calculations based on IMS Health MIDAS sales for MAT 09/2015 through MAT 09/2016.

For full prescribing information refer to the package insert approved by the Medicine Regulatory Authority

S1 **Neurobion® Tablets.** Each tablet contains Vitamin B_1 100 mg, Vitamin B_6 200 mg and Vitamin B_{12} 200 µg. Reg. No.: H2487 (Act 101/1965). S3 **Neurobion® Ampoules** Each 3 ml ampoule contains Vitamin B_1 100 mg, Vitamin B_6 100 mg and Vitamin B_{12} 1000 µg. Reg. No.: H2488 (Act 101/1965). Applicant: Merck (Pty) Ltd. Reg. No.: 1970/004359/07. 1 Friesland Drive, Longmeadow Business Estate South, Modderfontein, South Africa, 1645. Tel: +27 (0) 11 372 5000 / Fax: +27 (0) 11 372 5252. Report adverse events to drug.safety.southeastafrica@merckgroup.com or +27 (0) 11 608 2588 (Fax Line). SNA-NEU-1704-0094 May 2017.

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Medication

Certain chronic medications can increase risk for a Vitamin B deficiency.[18] These medications can decrease absorption, deplete stores, and increase clearance of the B vitamins.[3-7,18-21] See **Figure 2**. Higher doses and prolonged

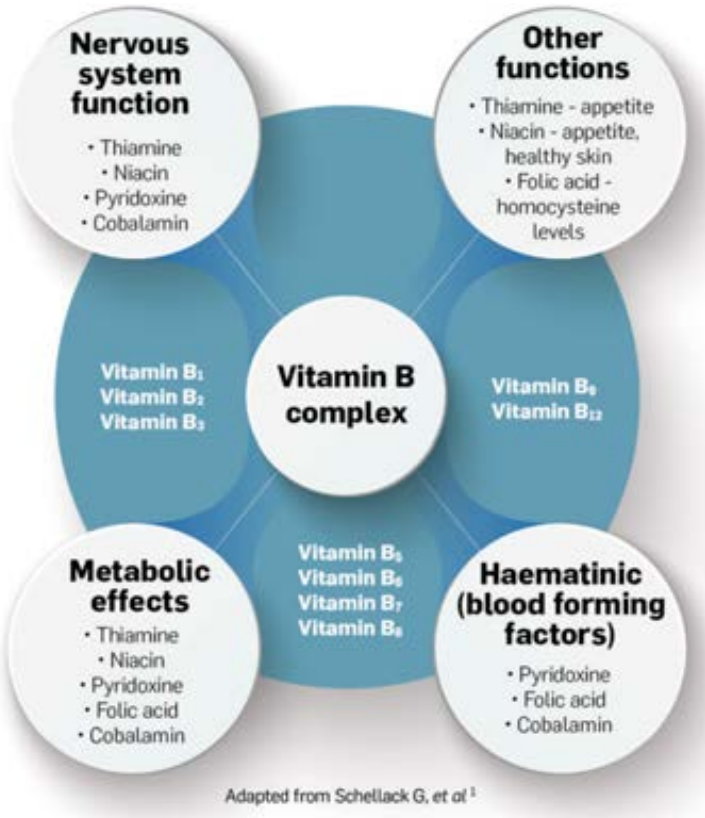


Figure 1. Simplified summary of some of the B-complex vitamins and their major areas of physiological functioning

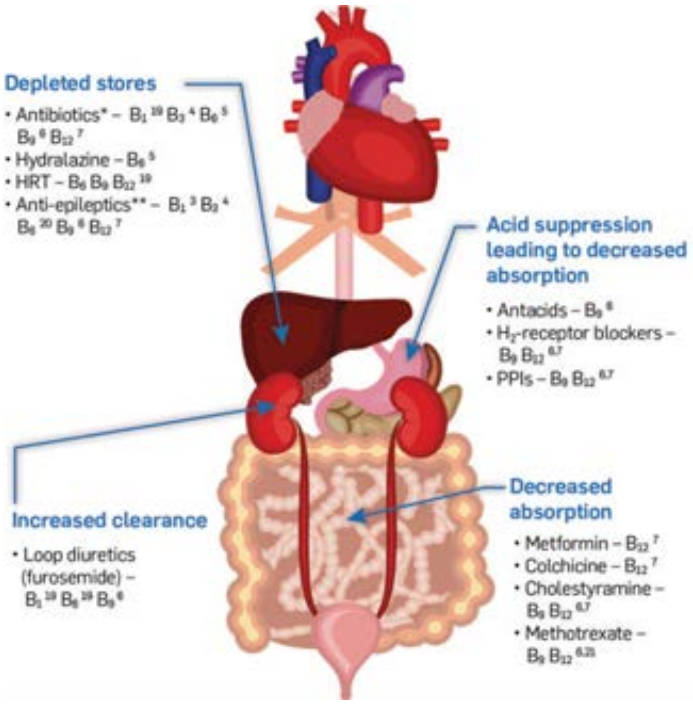


Figure 2. Medications that increase the risk of Vitamin B deficiencies.

Table 3. Causes of Vitamin B deficiencies in the elderly

Poor intake

- Poor health and increasing dependency [9,15]

Poor absorption

- Increased comorbidities and use of chronic medications that interfere with Vitamin B_{12} absorption e.g. metformin, H_2-receptor blockers, PPIs, antacids, cholestyramine[9,10]
- Increased prevalence of Pernicious Anaemia with advancing age[9]
- Atrophic gastritis (20-50% of elderly) with decreased acid-pepsin secretion and decreased release of protein bound Vitamin B_{12}[9]
- Overgrowth of bacteria, due to hypochlorhydria associated with atrophic gastritis, which bind Vitamin B_{12} for their own use[9]

Increased requirements

- Age-related metabolic changes and health problems can lead to increased requirements of B vitamins e.g. Vitamin B_6[15,16]

Increased excretion

- Use of diuretics can lead to the increased excretion of B vitamins e.g. Vitamin B_1[17]

administration (> 3 years) of metformin has been significantly associated with an increased risk of Vitamin B_{12} deficiency. [18] Although the exact mechanism is unknown, metformin is thought to compete with Vitamin B_{12} at the ileal receptor sites and thus decrease its absorption.[18] Gastric acid suppressive agents, such as H_2-receptor blockers and proton pump inhibitors, are another group of medications that are often used long-term and that have been linked to Vitamin B_{12} deficiency.[18] These medications cause a hypochlorhydric state, which results in malabsorption of protein-bound B_{12}.[18]

Malabsorption

As B vitamins cannot be manufactured by the body and are not stored in large amounts, they need to be ingested on a daily basis.[3-8,28] Gastrointestinal absorption of the B vitamins takes place mainly in the small intestine and there are many disorders that can negatively impact their uptake and result in deficiencies.[24,28-31] See **Figure 3**. Vitamin B_{12} specifically is absorbed through a complex process requiring normal functioning of several areas of the gastrointestinal tract.[18] Pepsin and hydrochloric acid separate free B_{12} from the protein bound B_{12} compound in the stomach. Free B_{12} then combines with R-proteins secreted from the salivary glands and gastric mucosa. This B_{12}-R-protein complex travels to the small intestine where free B_{12} is released by pancreatic enzymes in the alkaline environment. The released B_{12} then combines with intrinsic factor and passes through to the ileum where it is absorbed by the enterocytes.[18] Any alterations in the function and anatomy of the gastrointestinal tract such as gastric or ileal resection, inflammatory disorders, malabsorptive disorders, hypochlorhydria, a lack of intrinsic factor (pernicious anaemia) can therefore lead to Vitamin B_{12} malabsorption and deficiency.[18]

Excessive alcohol intake

Malnutrition and micronutrient deficiencies are common in chronic alcoholics.[32] 30-80% of alcoholics have thiamine deficiency, 50% have pyridoxine deficiency, 35% have niacin deficiency and 6-80% have folic acid deficiency.[32] Severe vitamin deficiencies (Vitamin B_1, B_3, B_6, and B_{12}) in chronic alcoholics may result in severe functional impairment and tissue damage, particularly in the brain.[32] Excessive alcohol consumption not only decreases the intake and absorption of B vitamins, but it also interferes with the storage, metabolism, utilisation and excretion of these vitamins.[32] See **Figure 4.**

HIV/AIDS

B vitamin deficiencies are widely seen in HIV, even in asymptomatic patients.[34,35] See **Table 4**. The B vitamin deficiencies in these patients are most likely due to the cachexia and catabolic state characteristic of AIDS.[36] In fact, HIV-infected patients require levels of B vitamins in multiples of the recommended

dietary allowance (RDA) to achieve normal plasma levels.[34] Malabsorption of Vitamin B_{12} occurs in HIV/AIDS patients and is due to many mechanisms including AIDS-related inflammation of the small intestine, gastric acid hyposecretion and production of antibodies to intrinsic factor.[34]

Diagnosis of vitamin B deficiencies

Severe deficiencies of some of the B vitamins may result in recognised disease entities such as pellagra, Beriberi and Wernicke's encephalopathy, megaloblastic anaemia and peripheral neuropathy.[1] However, the non-specific symptoms of milder deficiencies such as headache, confusion, weight loss, and fatigue may require a high index of suspicion to make an accurate diagnosis. See **Figure 5** for symptoms of B vitamin deficiencies. Multiple Vitamin B deficiencies are quite common.[1] Therefore, if at least one B vitamin is found to be deficient, other B vitamin deficiencies should be considered and excluded.[1] Also, a simple 'gold standard' diagnostic test may not be available – as is the case with Vitamin B_{12}.[9] When a B_{12} deficiency is suspected, the initial laboratory assessment includes serum B_{12} concentrations, a full blood count and a blood film examination to check for megaloblastic anaemia (which is often not seen in mild cases of B_{12} deficiency).[9] There is also no universally accepted serum Vitamin B_{12} cut-off to define deficiency – the WHO recommends the value of < 150 pmol/L, however, higher levels of 220 to 258 pmol/L based on more sensitive indicators of B_{12} status (raised homocysteine and MMA levels) have been suggested.[9] Refer to **Table 5** for diagnostics measurements for Vitamin B deficiencies.

Treatment

Active replacement treatment should be instituted in documented/diagnosed vitamin deficiencies. Since Vitamin B deficiencies

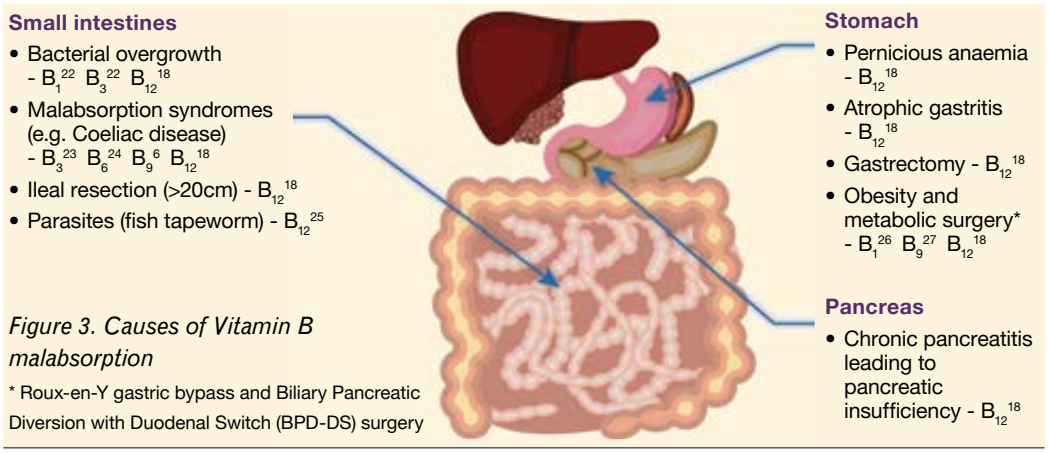
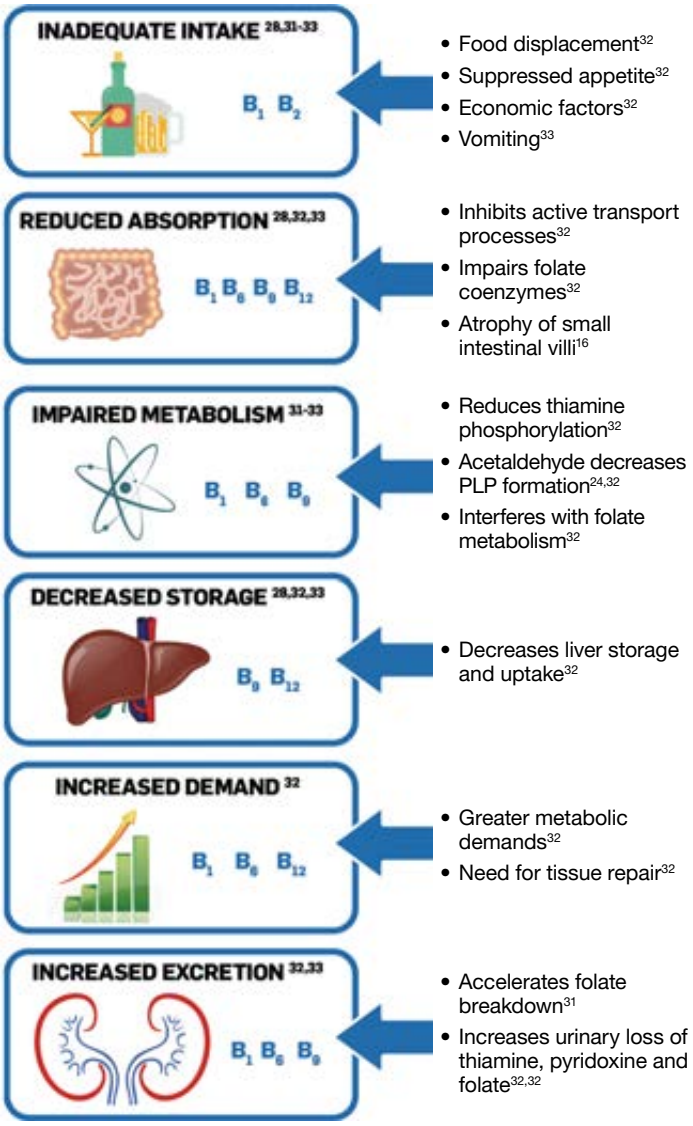


Figure 3. Causes of Vitamin B malabsorption

* Roux-en-Y gastric bypass and Biliary Pancreatic Diversion with Duodenal Switch (BPD-DS) surgery

Figure 4. Mechanisms of vitamin B deficiencies in chronic alcoholism



* Only at high alcohol intake levels

PLP = pyridoxal-5-phosphate (a coenzyme and active form of pyridoxine)

Table 4. Incidence of vitamin B deficiencies in HIV/AIDS

B Vitamin	Incidence of deficiency in clinical studies
B_1 (thiamine)	• 23% of patients with AIDS or AIDs-related complex[36] • 10% of patients with AIDS had Wernicke's encephalopathy at autopsy[28]
B_6 (pyridoxine)	• 34% of asymptomatic HIV patients[34] • 53% of CDC Stage III patients[34]
B_9 (folic acid)	• 41% of HIV-infected patients[37] • 64% of HIV-infected individuals at all stages of infection[34]
B_{12} (cobalamin)	10%-35% of patients with HIV/AIDS[34]

CDC = Centres for Disease Control and Prevention

Table 5. Diagnosing Vitamin B deficiencies

B Vitamin	Measurements
B_1 (thiamine)[28,38]	• TDP effect*: 15-25% for marginal deficiency >25% for deficiency • Direct measurement of erythrocyte TPP: <70nmol/L
B_3 (niacin)[39]	• Serum niacin <0,5µg/L
B_6 (pyridoxine)[16,24]	• Most common measure of vitamin B_6 status is serum PLP • PLP <20nmol/L
B_9 (folic acid)[31]	• Serum folate** <3ng/ml • Erythrocyte folate <140ng/ml • Increased homocysteine >16mmol/L
B_{12} (cobalamin)[9,30]	• Serum B_{12} <150pmol/L • Increased homocysteine >13mmol/L† • Increased MMA >0,4mmol/L • Full blood count and blood film examination showing megaloblastic anaemia

* TDP effect reflects the extent of unsaturation of transketolase enzyme with thiamine diphosphate, the main metabolically active form of thiamin (also known as thiamine pyrophosphate).[28] Now considered an inadequate method as it is nonspecific and less sensitive than erythrocyte TPP[38]

** Sensitive to diet, so may not reflect long-term status. † Not specific to Vitamin B_{12} deficiency as affected by low Vitamin B_6 and B_9 levels. TPP = thiamine pyrophosphate, PLP = pyridoxal 5' phosphate, MMA = methylmalonic acid

Table 6. Treating Vitamin B deficiencies

B Vitamin	Replacement Therapy
B_1 (thiamine) [1]	*Mild polyneuropathy* • 10-20mg orally, once daily, for two weeks *Moderate or advanced polyneuropathy** • 20-30mg orally, once daily, for several weeks after the symptoms disappear *Cardiovascular beriberi* • 100mg IV, once daily for several days *Wernicke-Korsakoff syndrome* • 50-100 mg IM or IV, twice daily, for several days • Then 10-20mg orally, once daily, until therapeutic response obtained
B_3 (niacin)[1]	• 250-500mg daily orally, in divided dosages 3-4 times a day or 100mg 8 hourly
B_6 (pyridoxine)[1]	• 50-100mg orally, once daily
B_9 (folic acid)[1]	• 400-1000µg orally, once daily • The normal requirement is 400µg per day
B_{12} (cobalamin)[1]	• Mild deficiency or no neurological symptoms and signs • 1000-2000 mg orally, once daily • Severe deficiency or neurological symptoms and signs • I mg IM, 1-4 times per week for several weeks, then given once a month for severe deficiency

IV = intravenously, IM = intramuscularly

* Neuropathy will not respond to treatment if the nerve cells have died off

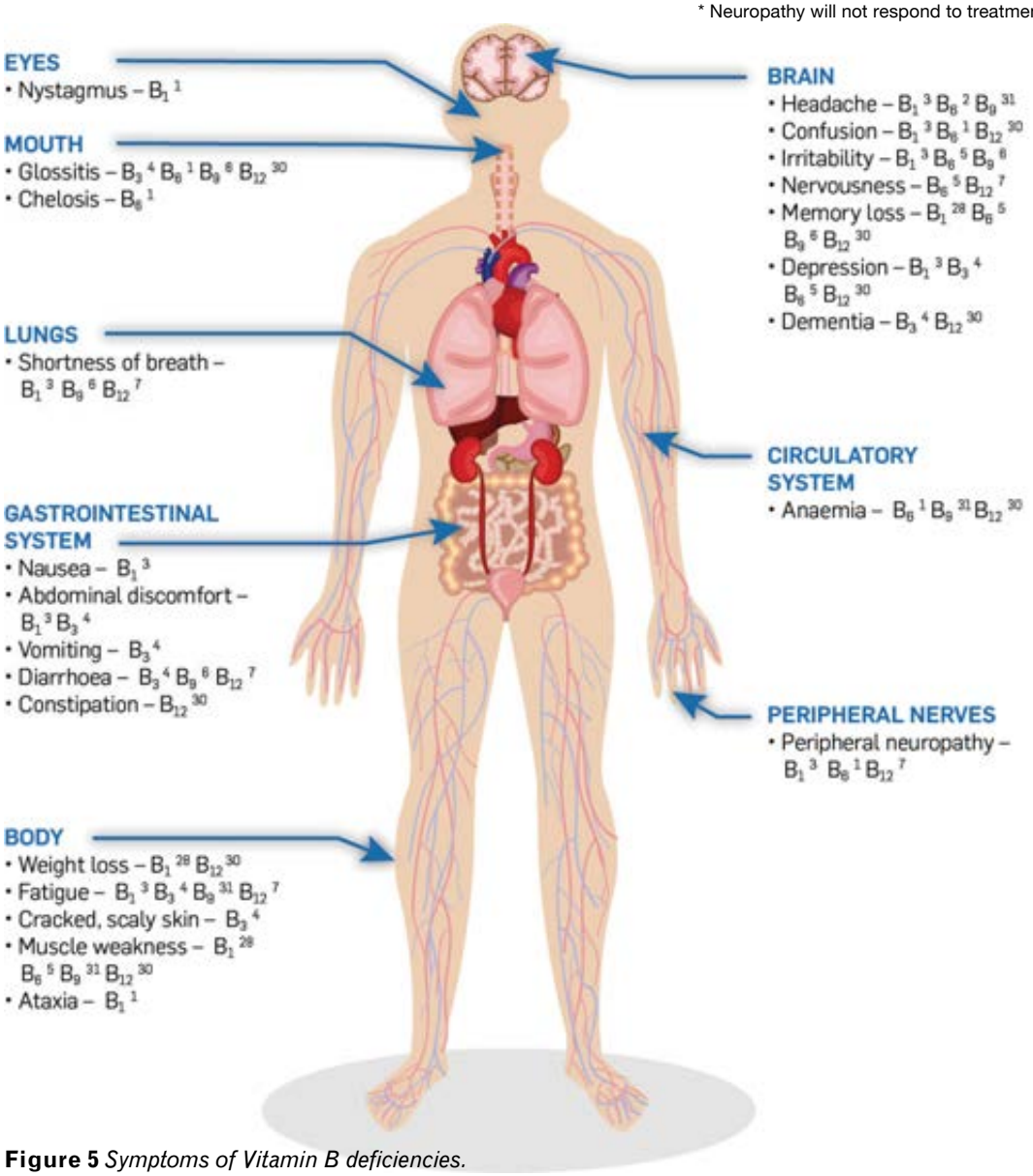


Figure 5 *Symptoms of Vitamin B deficiencies.*

seldom occur in isolation, multiple deficiencies should be suspected and investigated.[1] In cases where underlying conditions or chronic medication usage places patients at continued risk, there should be ongoing vitamin replacement therapy.[18] The stricter control of vitamin treatments and supplements by the Medicine Control Council (MCC) puts decision-making and treatment protocol back into the hands of the healthcare professional, who is best able to diagnose deficiencies, manage and monitor patient's progress. See **Table 6** for guidelines.

Conclusion

B vitamins are essential for important physiological functions and are significant contributors to the maintenance of optimal health.[1] Generally, a well-balanced diet will prevent Vitamin B deficiencies; however certain conditions and/or the use of chronic medication may predispose patients to low vitamin levels.[1,3-7] Active treatment should be instituted in documented/diagnosed vitamin deficiencies. In cases where underlying conditions or chronic medicine usage places patients at continued risk, there should be ongoing vitamin replacement therapy.[18]

References available on request. SF

Multiple choice questions

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1 The B-group (or B-complex) vitamins act as important co-enzymes in numerous metabolic processes and help the body convert carbohydrates into glucose for energy production, as well as to metabolise proteins and fats.

a. True A
b. False B

2 Some of the B vitamins are involved in the synthesis of _____ such as RNA and DNA.

a. Red blood cells, nerve transmitters and nucleic acids A
b. White blood cells, neurotransmitters and stomach acids B
c. White blood cells, neurotransmitters and nucleic acids C
d. Red blood cells, neurotransmitters and nucleic acids D

3 There are _____ essential B vitamins that cannot be synthesised in the body and hence need to be ingested daily.

a. Eight A
b. Seven B
c. Five C
d. Ten D

4 A well-balanced diet, including both plant and animal based foods, will prevent the occurrence of Vitamin B deficiencies.

a. True A
b. False B

5 Increased comorbidities and use of chronic medications that interfere with Vitamin B12 absorption e.g. _____, H2-receptor blockers, PPIs, antacids, cholestyramine.

a. Magnesium A
b. Metformin B
c. Potassium C
d. Methadone D

6 Gastrointestinal absorption of the B vitamins takes place mainly in the large intestine and there are many disorders that can negatively impact their uptake and result in deficiencies.

a. True A
b. False B

7 _____ of alcoholics have thiamine deficiency

a. 30-50% A
b. 20-50% B
c. 30-80% C
d. 20-80% D

8 Severe deficiencies of some of the B vitamins may result in recognised disease entities such as pellagra, Beriberi and Werner's encephalopathy, megaloblastic anaemia and peripheral neuropathy.

a. True A
b. False B

9 There is also no universally accepted serum Vitamin B12 cut-off to define deficiency – the WHO recommends the value of < _____ pmol/L.

a. 150 A
b. 200 B
c. 220 C
d. 300 D

10 B vitamin deficiencies are widely seen in HIV, even in asymptomatic patients.

a. True A
b. False B

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