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B Vitamin Complex and Chemotherapy-Induced Peripheral Neuropathy

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Abstract
Purpose of Review The purpose of this mini review is to evaluate the literature on B vitamins and chemotherapy-induced peripheral neuropathy.
Recent Findings One hundred and five journal articles were evaluated and nine manuscripts were included. There was one in vitro, one was an animal and seven were human studies. The in vitro study was a safety study on vitamin B_6 and oxaliplatin which was not directly related to CIPN. The animal study evaluated vitamin B_3 on paclitaxel administration with positive results. The human studies varied using a vitamin B complex, vitamin B_{12} only and vitamin B_6.
Summary Chemotherapy-induced peripheral neuropathy (CIPN) continues to plague patients and the medical fraternity. Currently, there are still no conclusive protective or treatment options. B vitamins have been found to play a role in CIPN prevention, but further studies are required to ascertain possible protection and treatment options.

Keywords B vitamins · Chemotherapy-induced peripheral neuropathy · CIPN · Vitamin B_{12}

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most dose-limiting side effects of chemotherapy administration. Currently, it is estimated that up to 90% of cancer patients experience CIPN at some stage during or after chemotherapy treatment with 30% continuing to suffer permanently [1]. To date, there is no effective CIPN prevention or treatment strategy.

CIPN is predominantly known to cause sensory neuropathy (numbness and tingling); however, motor (dropping things, difficulty walking) and autonomic changes (sweating) can also be experienced by patients [2]. Neuropathic pain is rarely experienced, even in cases of severe sensory CIPN. Symptoms experienced in the hands required separate evaluation to those experienced in the feet. This is due to the fact that the symptoms experienced in the upper body may be very different to those experienced in the lower body and vary depending on the patient and the chemotherapy agent administered [2].

There are many challenges with CIPN including diagnostic techniques, the unknown mechanism of action and the lack of effective preventative and treatment strategies. Researchers and clinicians continue to experiment with the various agents in order to attempt to prevent this disabling side effect due to the ongoing consequences experienced by cancer survivors.

One of the agent's trialled for prevention is the nutraceutical vitamin B complex and various individual B vitamins. Both animal and human clinical trials have been conducted, although the research to date is limited.

Vitamin B Complex and Peripheral Neuropathy

The B group vitamins include thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), cobalamin

(B_{12}), folate, choline and biotin. These vitamins all function within the nervous system as coenzymes in their activated state for numerous intermediary metabolic pathways including neurotransmitter synthesis and neuronal membrane synthesis [3]. Deficiencies in B group vitamins can occur due to a variety of reasons such as diet insufficiency, nutrient malabsorption and medication-induced vitamin deficiency such as metformin and vitamin B_{12} [4]. A deficiency in certain B group vitamins such as B_1, B_6 and B12 in addition to excess of vitamin B_6 is associated with nerve dysfunction and nerve damage that can lead to peripheral neuropathy [5••, 6••, 7].

Vitamin B_{12} in particular has been found to have an association with peripheral neuropathy and neuropathic pain particularly in advanced malignancy [5••]. The main difference between a traditional vitamin B_{12} deficiency and chemotherapy exposure is the time duration. In most cases, a vitamin B_{12} deficiency takes a long time to develop; however, recent studies have found that vitamin B_{12} can decrease rapidly during chemotherapy exposure [5••, 8, 9]. While this may be a transient deficiency or insufficiency, it could be a major causal factor for the development of CIPN in patients undergoing treatment with neurotoxic chemotherapy agents. Currently, very few cancer patients have their vitamin B_{12} or B_6 status checked prior to the commencement of chemotherapy.

Methods

A mini review was conducted on B group vitamins and CIPN. The eligibility criteria included studies conducted on B group vitamins and chemotherapy-induced peripheral neuropathy in animal, in-vitro and human studies. No critical appraisal tool was utilised nor risk of bias.

Search Terms

The search terms utilised for the search included ("B vitamin" OR "Vitamin B12" OR "methylcobalamin" OR "cobalamin" OR "pyridoxine" OR "thiamine") AND ("Chemotherapy-induced peripheral neuropathy" OR CIPN).

Databases

The databases selected included Pubmed, Scopus, EMBASE, EBSCO and AMED.

Time Frame

The dates for the search were selected as 1990 to 2017.

Results

One hundred and five journal articles were identified through the database and manual search, and nine met the inclusion criteria. Three manuscripts were excluded as they were duplicates. After title extraction, 17 journal articles were included, and 85 were excluded due to studies using other agents such as acetyl-L-carnitine or lipoic acid (n = 54) or only reporting on chemotherapy agents causing CIPN (n = 31). Abstract extraction showed 11 journal articles included, with 6 being excluded due to not being original research (n = 5) and one which excluded participants who had a B_{12} deficiency and not including any vitamin intervention. The full text extraction excluded two more journal articles due to mid-term publication of results and one being a conference presentation, leaving nine journal articles for review. See Fig. 1 for Prisma P diagram.

The journal articles identified included in vitro (n = 1), animal studies (n = 1) and human studies (n = 7) (see Table 1). The in vitro study was a safety assessment of pyridoxine (vitamin B_6) on cell lines with exposure to oxaliplatin. They found no reduction in the anti-tumour effect from

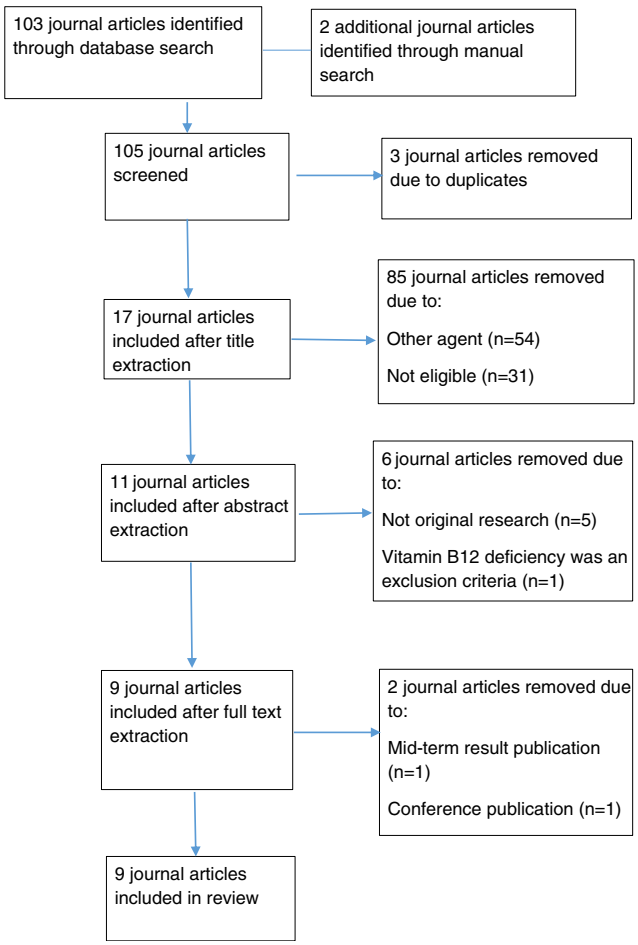

Fig. 1 PRISMA P diagram of review extraction for B vitamin complex and chemotherapy-induced peripheral neuropathy

Table 1 Journal articles for B vitamin complex and chemotherapy-induced peripheral neuropathy

Author	Year	Type of study	B vitamin	Chemotherapy agent	No of participants	Result
Cell line						
Garg MB, Ackland SP. [10]	2011	Cell culture	Vitamin B_6	Oxaliplatin		Addition of pyridoxine at concentrations of 1–25 muM did not affect cytotoxicity of oxaliplatin therefore does not reduce anti-tumour effect. Possible protection for CIPN.
Animal studies						
Hamity MV, White SR et al. [11]	2017	Rat study	Vitamin B_3 (nicotinamide)	Paclitaxel		200 mg/kg of nicotinamide beginning 7 days before paclitaxel administration and 24 days post-prevented the tactile hypersensitivity and blunted place escape-avoidance behaviours. The effects were sustained for 2 weeks and did not interfere with anti-tumour effect. Acetyl-L-carnitine did not prevent either and actually produced tactile hypersensitivity. Treatment with 200 mg/kg of nicotinamide for 3 weeks after paclitaxel reversed the well-established tactile hypersensitivity and escape-avoidance behaviours.
Human studies						
Wiernik PH, Yeap B, et al. [12]	1992	RCT	Vitamin B_6	Cisplatin, HMM	248	Pyridoxine administration of 300 mg orally from day 1–21 significantly reduced the neurotoxicity but was found to interfere with response duration.
Rostock M, Jaroslawski K, et al. [13]	2013	RCT	Vitamin B_1, B_6	CIPN from various agents	14	Four-arm trial on cancer patients with CIPN. $n = 14$ with electric acupuncture, $n = 14$ with hydroelectric baths, $n = 15$ with vitamin B_1/B_6 (30 mg/300 mg daily), $n = 17$ placebo. No significant differences were noted for all groups compared to placebo.
Hirayama Y, Ishitani K, et al. [14••]	2015	Open label crossover RCT	Vitamin B_{12} versus duloxetine	Taxane or platinum-based CIPN	34	Group A received duloxetine 20 mg/day orally for 1 week, than 40 mg/day for the next 3 weeks. Group B received vitamin B_{12} 1.5 mg/day orally for 4 weeks. After 2- to 4- week washout period, treatment was crossed over for another 4 weeks. Duloxetine was superior to B_{12} for numbness ($p = 0.03$) and pain reduction ($p = 0.04$).
Schloss JM, Colosimo M, et al. [9]	2015	Case study	Vitamin B_{12} and B complex	Paclitaxel	1	A case study on a patient in a trial showed vitamin B_{12} deficiency post-taxane chemotherapy with grade 3/4 CIPN. Administration of IM vitamin B_{12} and a vitamin B complex for 3 months reversed CIPN to Level 1 (in finger tips and top of toes).
Soloman L. [5••]	2016	Retrospective study	Vitamin B_{12}		241	Palliative care patients with CIPN and neuropathic pain were evaluated for functional vitamin B_{12} deficiency through homocysteine and MMA and B_{12} status. B_{12} therapy decreased MMA and improved neurologic symptoms.
Schloss JM, Colosimo M, et al. [15]	2017	RCT	B vitamin Complex	Paclitaxel, vincristine, Taxol/carboplatin	71	Placebo controlled trial assessing the protective effect of B vitamins for CIPN. A trend was observed, particularly for vitamin B_{12} in reducing the onset and severity, but no statistical significance on the TNS was found. Significance was found for patient reported reduced sensory CIPN with the B vitamin complex.
Han X, Wang L, et al. [16]	2017	RCT	Vitamin B_{12}	CIPN treatment after multiple myeloma Tx	104	Patients randomised into: Group A: 500mcg IM methylcobalamin every second day for 20 days followed by 2 months of 500mcg oral methylcobalamin TDS (1.5 mg/day) Group B: acupuncture combined with methylcobalamin (same regime). Results found the combination of acupuncture and methylcobalamin showed a better outcome than methylcobalamin alone.

the oxaliplatin and surmised that vitamin B_6 trials as a protective agent could be beneficial as it did not interfere with treatment [10].

The animal study by Hamity MV et al. (2017) conducted a well-structured trial on rats assessing both the protective and treatment ability of nicotinamide (vitamin B_3). They found that nicotinamide was both protective and a treatment option for tactile hypersensitivity (sensory neuropathy) and escape-avoidance behaviour (motor) from administration of paclitaxel [11].

Of the human studies, five out of seven were randomised controlled trials (RCTs) [12, 13, 14••, 15, 16], one was a case study [9] and the other a retrospective study [5••]. Four studies examined vitamin B_{12} for either protective or treatment options [5••, 9, 14••, 16], two studies examined vitamin B_6 [12, 13], one study combined vitamin B_6 with B_1 [13] and one used a B group vitamin complex in a protection study [15].

Two studies were protection studies. One assessed vitamin B_6 [12] with cisplatin and HMM with the results finding it to be statistically significant in the prevention of CIPN; however, it affected dose response. The second study examined a B group vitamin [15] for the prevention of CIPN from paclitaxel and vincristine administration. The results were not statistically significant but noticed a trend towards a reduction in onset and severity, particularly with vitamin B_{12}. Three studies were comparative effectiveness studies for treatment of CIPN [13, 14••, 16]. The first one compared duloxetine to vitamin B_{12} in a crossover trial and found that duloxetine was superior to vitamin B_{12} for numbness and pain reduction [14••]. The second one was a four-arm study assessing electro-acupuncture, hydroelectric baths and vitamin B_1/B_6 to placebo for treatment. None were found to be statistically significant compared to placebo [13]. And lastly, vitamin B_{12} was compared to vitamin B_{12} and acupuncture for treatment of CIPN from multiple myeloma treatment which found the combination of vitamin B_{12} and acupuncture superior to vitamin B_{12} alone [16].

Discussion

To date, both treatment and protection of CIPN is limited. The fact that each chemotherapy agent has a different mechanism of action of which, the causation of the CIPN from these drugs are not conclusive; each patient varies biochemically and physiologically; and each patient responds differently to medication, and supplementation makes it difficult for clinicians to find agents to protect against this debilitating side effect.

In regard to the B vitamins, there is no conclusive evidence of protection or treatment of CIPN. However, there is evidence to show that B vitamins can influence and possibly protect some patients against CIPN development or the onset and severity of CIPN. Vitamin B_3, B_6 and B_{12} show potential in assisting patients by protecting against this side effect, but further studies are required. In addition, there is a possibility that patients who are deficient in vitamin B_{12} post-chemotherapy and who present with moderate to severe CIPN can benefit from B_{12} administration. Vitamin B_3 shows potential in animal studies and required human trials to confirm its beneficial protective ability.

Many studies have been conducted on CIPN [17] with limited success. As trials continue, combining therapies may show increased benefits for patients in the prevention of this side effect. Identifying what has been trialled for each chemotherapy or immunotherapy agent that causes CIPN and combining those which have either shown statistical significance or a trend in the right direction, might be worthwhile. Continuing research into identifying the mechanism of action of these drugs on CIPN development is also imperative, as is studying why certain patients get CIPN and others do not.

CIPN continues to plague patients and the medical fraternity, and currently, there are still no conclusive protective or treatment options. Taking into consideration all the studies that have been conducted, both protection and treatment options will depend on that person, as not one agent seems to be beneficial for everyone. The literature needs to be critically evaluated, and options for protection against each chemotherapy agent need to be assessed for each patient. For most of the studies, only one agent has been trialled, although when two therapies were combined, such as vitamin B_{12} and acupuncture [16], it was found that they were superior to one therapy alone.

Conclusion

CIPN is a debilitating side effect with limited protective or treatment options for patients. No one single agent has been found to be completely protective against this side effect; similarly, no treatment options work for everyone. What may be found in the future is that a combination of therapies may be more effective than single agents in the prevention of CIPN. In conclusion, B vitamins play a role in CIPN but further studies are required to ascertain to what extent, and if used in combination with other therapies, agents or nutrients, provide a protection or treatment option for various neurotoxic chemotherapy and immunotherapy agents.

Vitamin B_{12} is encouraged to be tested in patients undergoing chemotherapy with neurotoxic agents before the commencement of chemotherapy treatment and at the onset of moderate CIPN development. Further studies on vitamin B_6 and vitamin B_3 are required on humans in both dose-dependent and drug-specific trials. Supplementation with B vitamins has been shown to not interfere with efficacy of the chemotherapy drugs except for high doses of vitamin B_6. Hence, the use of a B complex during chemotherapy is

considered to be safe, a cheap option for patients with possible preventative effects for CIPN development. If patients are unable to take an oral B vitamin complex, vitamin B_{12} or B vitamin injections might be an alternative option for these patients. Possible prevention may be better than no prevention options at all.

Compliance with Ethical Standards

Conflict of Interest Janet Schloss and Maree Colosimo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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