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Post-Marketing Surveillance of Fixed Dose Combination of Methylcobalamin, Alpha Lipoic Acid, Folic Acid, Biotin, Benfotiamine & Vitamin B6-Nutripathy for the Management of Peripheral Neuropathy

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Abstract

***Background*: Peripheral neuropathy is a commonly encountered troublesome condition which is often disabling & worsens when left untreated. Traditional neuropathic pain medications primarily provide symptomatic relief; however, the pathogenesis of nerve damage remains unresolved. Extensive literature survey reveals that patients with peripheral neuropathy experience significant benefits with the use of B-vitamins like methylcobalamin (B12), folic acid (B9), biotin (B7), benfotiamine (B1) and pyridoxine (B6). The other well documented antineuropathic agents include alpha lipoic acid, glutathione, omega fatty acids, myoinositol, certain trace elements, etc. *Materials and Methods*: A multicentre, prospective, open-label, non-comparative clinical study was carried out in 497 patients with peripheral neuropathy. A fixed dose combination of methylcobalamin, alpha lipoic acid (ALA), folic acid, biotin, benfotiamine & vitamin B6 capsule was orally administered once daily for 12 weeks. *Results*: Treatment led to significant reduction from baseline score in various neuropathy symptoms from the 4th week itself. After 12 weeks of treatment, the mean pain score declined by 78.0%, numbness by 92.1% and muscle weakness by 96.9%. Also, there was 96.0% & 99.2% reduction in tingling & burning sensation respectively. No serious adverse events were reported. *Conclusion*: The current study confirms that fixed dose combination of methylcobalamin, ALA, folic acid, biotin, benfotiamine & vitamin B6 is effective & well tolerated in the management of peripheral neuropathy.**

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Keywords

Peripheral Neuropathy, Methylcobalamin, Alpha Lipoic Acid, Folic Acid, Biotin, Benfotiamine, Vitamin B6

1. Introduction

Peripheral neuropathy (PN) is a progressive disease with high prevalence worldwide. In the broadest sense, peripheral neuropathy refers to a range of clinical syndromes affecting a variety of peripheral nerves, including motor, sensory and autonomic fibres [1]. Diagnosis of peripheral neuropathy depends on the recognition of signs and symptoms which encompasses sensory and motor deficits. Often, in diabetes, the symptoms are symmetrical and involve hands and feet with "glove and stocking" distribution [2]. It is characterized by debilitating outcomes like pain, numbness, burning and tingling in the extremities; slowed nerve conduction; loss of balance, reduced vibration perception threshold & decreased tendon reflexes.

Nutritional deficiency has a great influence on nervous system because optimal functioning of the central and peripheral nervous system is dependent on a constant supply of appropriate nutrients [3]. The State of Food Insecurity in the World estimated that almost 870 million people were chronically undernourished in 2010-12 [4]. It is not uncommon that conditions like old age, eating disorders, diabetes, gastrointestinal diseases, alcohol abuse, etc. are characterized by multiple nutritional deficiencies and these conditions are linked to peripheral neuropathy as well [3]. Further, even the post harvesting processing has led to emergence of crops that are not very nutritionally appropriate. Hence, the presumed balanced diet may not suffice the nutritional requirement [5].

The correlation between nutrition and peripheral neuropathy dates back to 19th century based on the epidemic of polyneuropathy and heart failure due to beriberi [6]. The strong evidence is bariatric surgeries leading to nutritional deficiencies and consequent neurologic problems [7] [8]. Also, it is well documented that neurologic symptoms are the earliest and often the only manifestation of cobalamin deficiency [9].

Nutripathy, the science that deals with nutritional management of diseases, has proven significant benefits in treatment of peripheral neuropathy. Being a multifactorial complication, resolution of peripheral neuropathy demands a multinutrient treatment approach. It is well accepted that B-vitamins are required for optimum functioning of nervous system in combination with antioxidants [3] [10]-[16]. Methylcobalamin, the active form of vitamin B12, helps in the formation of methionine from neurotoxic homocysteine; methionine, in turn, is required for methylation reactions associated with myelin sheath & neurotransmitter formation. Folic acid participates in DNA synthesis and a range of metabolic and nervous system biochemical processes. Benfotiamine, a fat soluble analogue of thiamine, increases transketolase activity involved in glucose metabolism. As a result, it blocks the pathways leading to hyperglycemic damage to nerves. Unavailability of biotin & thiamine decreases the activity of various enzymes associated with pyruvate metabolism, thus resulting in neurotoxic pyruvate accumulation. Also, biotin has shown to inhibit hyperglycemia induced damage to peripheral nerves. Vitamin B6 metabolizes neurodamaging homocysteine via cystathione pathway and nerve conduction studies reveal severely reduced sensory nerve action potentials in vitamin B6 deficient patients. Also, nerve biopsy of subjects with pyridoxine deficiency confirms axonal degeneration of small and large myelinated fibers. Antioxidant like alpha lipoic acid (ALA) has shown its efficacy in neuroprotection by scavenging a wide range of reactive oxygen species.

The present study was a post-marketing surveillance (PMS) conducted to evaluate the safety and efficacy of once daily administration of fixed dose combination comprising of methylcobalamin, ALA, folic acid, biotin, benfotiamine and vitamin B6 for the treatment of peripheral neuropathy.

2. Materials and Methods

2.1. Design of Investigation

This PMS included 497 patients with peripheral neuropathy and was conducted at 5 different centers by qualified investigators. The efficacy of the treatment was assessed based on improvement in parameters like neuropathic

pain, numbness, muscle weakness, tingling and burning. Investigation of parameters was performed throughout the treatment period on: visit I (baseline), visit II (week 4), visit III (week 8) and visit IV (week 12). Demographic data, medical history, previous treatment and physical examination data were collected from all patients during the first visit. Also at the end of the treatment, global assessment of efficacy and tolerability was confirmed by the physicians and patients as well.

2.2. Patients' Selection

Inclusion Criteria: Male or female patients 18 years of age or older with peripheral neuropathy.

Exclusion Criteria: Pregnant or lactating women, patients with history or presence of psychiatric disorders and patients with contraindication to methylcobalamin, ALA, folic acid, biotin, benfotiamine or vitamin B6.

2.3. Study Medication

Patients with peripheral neuropathy were orally administered fixed dose combination of methylcobalamin 1500 mcg, ALA 200 mg, folic acid 5 mg, biotin 5 mg, benfotiamine 50 mg & vitamin B6 5 mg once daily for 12 weeks.

2.4. Study Endpoints and Measures of Outcome

The efficacy of the combination was evaluated at week 4, 8 and 12 based on the change in neuropathy symptom scores from baseline. Neuropathic pain was graded on a 10 point scale: 0 = no pain, 1 - 2 = mild pain, 3 - 4 = moderate pain, 5 - 6 = severe pain, 7 - 8 = very severe pain, 9 - 10 = worst pain. Other symptoms like numbness, muscle weakness, tingling and burning were also scored as: 0 = Absent, 1 = Mild, 2 = Moderate and 3 = Severe. The global assessment of efficacy of treatment was done by physicians and patients at the end of the study which was based on the scale: 1 = very good improvement, 2 = good improvement, 3 = moderate improvement, 4 = negligible improvement. Evaluation of safety was depending on the occurrence of any adverse event (AE) and was graded based on the severity, onset and the course of adverse effects. Global assessment of tolerability was done by physicians and patients towards the end of the study which was evaluated using the scale: 1 = excellent, 2 = good, 3 = fair, 4 = poor.

2.5. Statistics

The data was pooled & the results were analyzed using parametric and non-parametric tests. All tests were two tailed & $p < 0.05$ was considered significant.

3. Results

A total of 497 cases were evaluated in the study. The overall demographic profile of the patients is presented in **Table 1**. The physical examination parameters such as temperature, pulse rate, respiratory rate and blood pressure were within normal limits at baseline as shown in **Table 2**.

3.1. Effect on Pain Intensity

Mean score of pain at baseline was 5.50. A substantial difference in pain intensity was observed after the study treatment. After 4, 8 & 12 weeks, the mean score of pain showed a significant fall of 34.9%, 58.7% & 78.0% respectively from baseline, $p < 0.05$ (**Figure 1**).

3.2. Effect on Numbness Score

At the start of the treatment, mean score of numbness was 2.16. At the end of week 4, 8 & 12; the mean score of numbness showed a reduction of 44.0%, 82.9%, and 92.1% respectively, which was statistically significant, $p < 0.05$ (**Figure 2**).

3.3. Effect on Muscle Weakness

The mean baseline score of muscle weakness was analyzed to be 1.61. A significant decline of 29.2%, 71.4%

Table 1. Summary of patient demographic data.

No. of Cases	497
Age (years)	
Mean	55.18
SD	8.12
Range	40 - 75
Weight (kg)	
Mean	67.58
SD	9.00
Range	43 - 88
Sex (%)	
Male	308 (62.0)
Female	189 (38.0)

Table 2. Baseline values of physical examination parameters.

Parameters	Mean ± SD (N = 497)
Temperature (˚F)	97.94 ± 0.59
Pulse Rate (/min)	77.18 ± 4.87
Respiratory Rate (/min)	17.42 ± 1.65
SBP (mmHg)	124.96 ± 6.94
DBP (mmHg)	84.54 ± 5.07

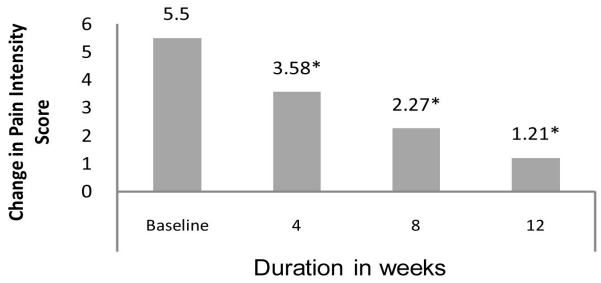


Figure 1. Change in mean pain score ($^{*}p < 0.05$).

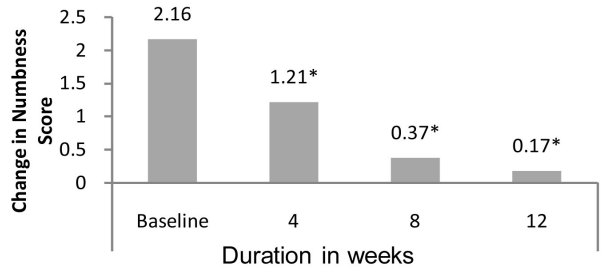


Figure 2. Change in mean numbness score ($^{*}p < 0.05$).

and 96.9% from baseline score of muscle weakness was noticed at the end of week 4, 8 and 12 respectively. The change in mean score of muscle weakness was found to be statistically significant, $p < 0.05$ (**Figure 3**).

3.4. Effect on Tingling Symptom

At baseline the mean score of tingling was recorded to be 1.76. After 4 weeks, the mean score of tingling showed a fall of 46.6% which was statistically significant from baseline. After 8 weeks, tingling score further decreased by 92.6% and after 12 weeks, a decline of 96.0% was observed, $p < 0.05$ (**Figure 4**).

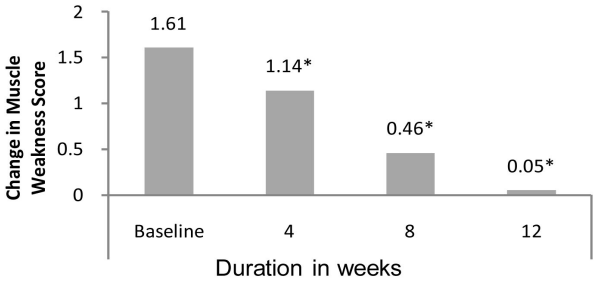


Figure 3. Change in mean muscle weakness score ($^{*}p$ <0.05).

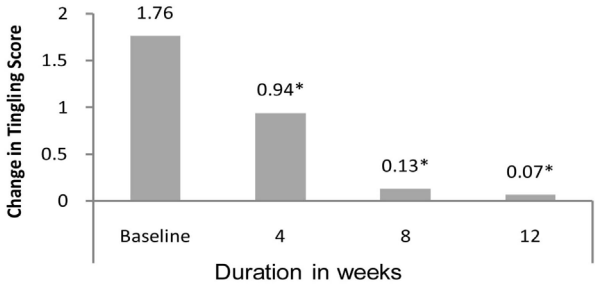


Figure 4. Change in mean tingling score ($^{*}p < 0.05$).

3.5. Effect on Burning Sensation

Mean burning score before treatment initiation was recorded as 1.23. After 4 weeks, the mean score of burning lowered considerably by 61.8%. After 8 and 12 weeks, it showed a significant decrease of 87.0% and 99.2% respectively, $p < 0.05$ (**Figure 5**).

3.6. Global Assessment of Efficacy of Treatment

As per physicians' evaluation, 90.3% of the cases showed very good and remaining showed good improvement after the treatment (**Figure 6(a)**). According to patients' evaluation, 92.4% of the patients had very good and 7.6% had good improvement after the treatment (**Figure 6(b)**).

3.7. Safety Assessment

This analysis reveals that 2.2% of the total cases had adverse events. The reported adverse effects include nausea, vomiting and abdominal pain. The intensity of these events was mild in all the cases, which resolved during the treatment. **Table 3** gives an overview of adverse events reported during study.

3.8. Global Assessment of Tolerability of Treatment

The overall global assessment of tolerability of treatment was conducted by physicians and patients. As per physicians' evaluation, 97.8% of the cases showed excellent and 2.2% had good tolerability of the treatment (**Figure 7(a)**) and according to patients' evaluation, 98.0% of them had excellent while 1.8% and 0.2% had good and fair tolerance respectively (**Figure 7(b)**).

4. Discussion

Peripheral neuropathy affects a substantial percentage of population and presents with significant morbidity. Pain in the fingers, toes, hands or feet is the most common symptom of neuropathy. The other frequently described symptoms of PN are numbness, tingling, burning, abnormal temperature perception, decreased muscle strength and compromised movement [17]. It can have extremely devastating consequences; patients experiencing PN report a reduced quality of life, chronic discomfort and disruption of physical abilities for general life activities.

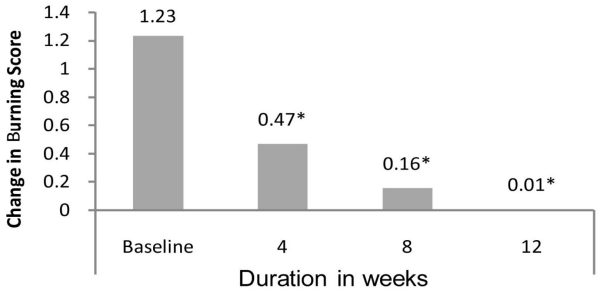
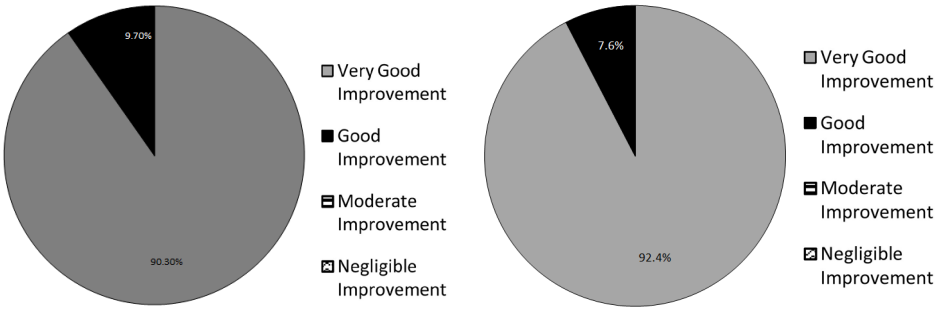


Figure 5. Change in mean burning score ($^{*}p < 0.05$).



(a) (b)

Figure 6. Overall global assessment of efficacy of treatment by physicians (a) and patients (b).

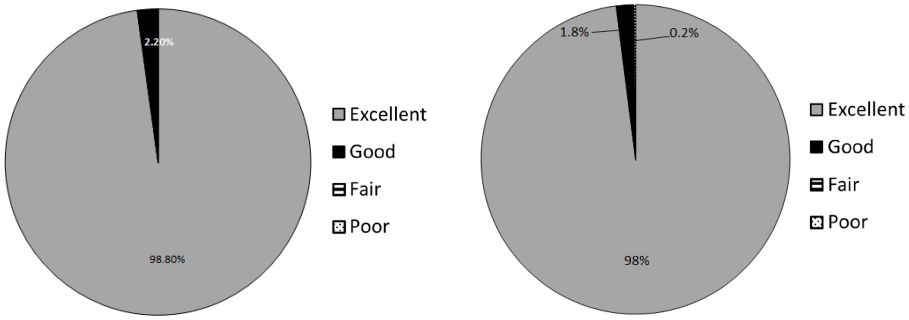


Figure 7. Overall global assessment of tolerability of treatment by physicians (a) and patients (b).

Table 3. Safety profile.

Adverse Events	No. of Cases (N = 497)	Percentage (%)
Abdominal Pain	4	0.8
Nausea	4	0.8
Vomiting	5	1.0
Number of Events	13	2.6
Total Number of Cases	11	2.2

Conventional neuropathy treatment includes tricyclic antidepressants, selective serotonin reuptake inhibitors, anticonvulsants, lidocaine patches, topical capsaicin, opioid and non-opioid analgesics. While these agents exhibit modest resolution of symptoms, low tolerability limits their long term use. Further, they merely mask the symptoms of neuropathy and do not address the underlying pathologies [18]. Aldose reductase inhibitors like epalrestat, is a promising class of drugs that tackles one of the pathogenic pathways of diabetic neuropathy [19]-[21].

The physiology of nervous system is considerably interrupted by nutritional deficiency itself [22]. Particularly important for efficient functioning of the nervous system are the B-group vitamins (vitamin B12, thiamine, niacin, folic acid and pyridoxine) [23]. Chronic B-vitamin deficient state leads to demyelination of axons and subsequently destruction of underlying axons. Occurrence of vitamin B derangement is the shared pathogenic mechanism in the varied etiologies of peripheral neuropathy viz. diabetes, certain medications, alcoholism, eating disorders, bariatric or gastrointestinal surgeries, malabsorptive states, HIV infection, etc. Hyperhomocysteinemia is an independent risk factor for peripheral neuropathy and it is stated that deficiency of vitamin B12, folate and pyridoxine results in elevated homocysteine levels [24]. Oxidative stress, too, is an identified cause of physical damage to neurons by demyelination, mitochondrial dysfunction, depletion of antioxidant defenses, neuroinflammation and neuronal death through apoptosis [25].

Unbalanced diet consumption, veganism, low economic status appears to be the most common reasons for dietary deficiency. Moreover, diabetes, malabsorption syndromes, depression, cancer, chronic infections and prolonged consumption of alcohol are among the other common predisposing factors. In addition, several drugs like metformin, isoniazid, PPIs, anticonvulsants, etc. have been found to interact with B-vitamin metabolism [26]-[29] and hence their long-term use may consequently result in nerve dysfunction. Thus, neuropathy develops as a late complication of nutritional deficiency in most of the patients.

Compromised peripheral nerve function may lead to impaired physical function and disability in patients with nutritional deficiency and hence, it is vital to combat the potentially modifiable risk factors. B-vitamin deficiency is a well-recognized risk factor for the disease of peripheral nervous system. Usually the deficiency is multifactorial; it is rare that deficiency of single B-vitamin is identified as the sole cause of neuropathy [23]. Thus, it trails that combination therapy aimed at correcting the pathogenic features of neuropathy such as disturbances in the synthesis of lipids needed for nerve tissue, oxidative stress, decreased neuronal blood supply, impaired neurotransmission, etc. has the potential to provide effective treatment for neuropathy.

B-vitamins and ALA are well researched treatment options for peripheral neuropathy [18]. Methylcobalamin has been extensively studied as a nerve regenerator leading to significant improvement in the symptoms of neuropathy [30] [31]. Analysis of controlled clinical trials of methylcobalamin by Yu Sun *et al.* revealed benefits in somatic symptoms such as pain and paresthesia as well as autonomic symptoms. In their previous work, M. Maladkar *et al.* reported faster and better resolution of symptoms with the combination of epalrestat and methylcobalamin compared to epalrestat alone in diabetic patients with PN [19]. In a double-blind, randomized, controlled clinical study, benfotiamine in combination with vitamin B12 and pyridoxine has demonstrated effectiveness against diabetic peripheral neuropathy. Neurotropic benfotiamine and other B vitamin combination has been suggested as first line treatment approach in management of diabetic PN [32]. Several clinical studies have confirmed the positive clinical effects of ALA on neuropathy symptoms [18] [33] [34].

In subjects with impaired neurological functions, folate deficiency was one of the abnormal parameters identified, thus confirming its role in neuropathy progression [35]. The efficacy of biotin has been verified in hemodialysis and diabetic patients with PN [36] [37]. Considerable improvement was noted with biotin treatment in paresthesia and difficulty in walking.

The present post-marketing surveillance study was undertaken to evaluate efficacy and safety of fixed dose combination of methylcobalamin, ALA, folic acid, benfotiamine, biotin and vitamin B6 in the management of PN. The observation items included reduction in neuropathic pain, numbness, tingling, burning sensation and muscle weakness.

The clinical assessment showed statistically significant ($p < 0.05$) change in bothersome symptoms of neuropathy *i.e.* pain, numbness, tingling and burning sensation with combination therapy. Favorable effects were exhibited within 4 weeks of study commencement and continued till end of treatment period. Treatment efficacy was rated as very good by the majority of both physicians and patients, thus ratifying the usefulness of combination therapy. Pain intensity decreased by 78% and more than 90% improvement in numbness, tingling and burning sensation was achieved at study completion.

Noteworthy improvement was demonstrated by the patients in physical activity limiting parameter *viz.* muscle weakness at all the visits during the study duration. Muscle weakness score reduced by approximately one-third at the first follow-up and further decreased by 96.9% at the end of treatment phase. The differences in the score from baseline were statistically significant ($p < 0.05$) throughout the treatment follow-up.

The beneficial effects of combination therapy were possibly due to enhancement in motor and sensory function by promoting myelin formation, axonal phospholipid synthesis, improvement in neuroconduction facilitated

by enhanced neurotransmitter synthesis and reduction in oxidative stress.

The combination was well tolerated with no major adverse effects being experienced by the patients. Commonly reported adverse effects were mainly gastrointestinal related; the intensity of these effects was described as mild and resolved during the course of treatment.

5. Conclusion

This clinical trial confirms the marked and clinically relevant effect of fixed dose combination of methylcobalamin, ALA, folic acid, biotin, benfotiamine and vitamin B6 on neuropathy symptoms in a real-life situation. Thus, it is a safe and effective option for the management of peripheral neuropathy.

References

[1] Bromberg, M.B. (2005) An Approach to the Evaluation of Peripheral Neuropathies. *Seminars in Neurology*, **25**, 153-159. http://dx.doi.org/10.1055/s-2005-871323

[2] John, C. P. and Gareth, W. (2003) Textbook of Diabetes 2. 3rd Edition, Blackwell Science Ltd., Oxford, 51.3.

[3] Hammond, N., Wang, Y.X., Dimachkie, M.M and Barohn, R.J. (2013) Nutritional Neuropathies. *Neurologic Clinics*, **31**, 477-489. http://dx.doi.org/10.1016/j.ncl.2013.02.002

[4] Food and Agriculture Organization of the United Nations (2012) The State of Food Insecurity in the World. Food and Agriculture Organization of the United Nations, Rome. http://www.fao.org/docrep/016/i3027e/i3027e.pdf

[5] Fitzpatrick, T.B., Basset, G.J., Borel, P., Carrari, F., DellaPenna, D., Fraser P.D., *et al*. (2012) Vitamin Deficiencies in Humans: Can Plant Science Help. *The Plant Cell*, **24**, 395-414. http://dx.doi.org/10.1105/tpc.111.093120

[6] Koike, H., Misu, K., Hattori, N., Ito, S., Ichimura, M., Ito, H., Hirayama, M., Nagamatsu, M., *et al*. (2001) Postgastrectomy Polyneuropathy with Thiamine Deficiency. *Journal of Neurology, Neurosurgery & Psychiatry*, **71**, 357-362. http://dx.doi.org/10.1136/jnnp.71.3.357

[7] Rudnicki, S.A. (2010) Prevention and Treatment of Peripheral Neuropathy after Bariatric Surgery. *Current Treatment Options in Neurology*, **12**, 29-36. http://dx.doi.org/10.1007/s11940-009-0052-2

[8] Alvarez, L. and Jacqueline, I. (2004) Nutrient Deficiencies Secondary to Bariatric Surgery. *Current Opinion in Clinical Nutrition & Metabolic Care*, **7**, 569-575. http://dx.doi.org/10.1097/00075197-200409000-00010

[9] Healton, E.B., Savage, D.G., Brust, J.C., Garrett, T.J. and Lindenbaum, J. (1991) Neurologic Aspects of Cobalamin Deficiency. *Medicine* (*Baltimore*), **70**, 229-245. http://dx.doi.org/10.1097/00005792-199107000-00001

[10] Tammy, J.L., Kirsten, V., Michael, T. and Christopher, M.H. (2012) Diabetic Neuropathic Pain: Real World Treatment Options. *Clinical Medicine Insights*: *Therapeutics*, **4**, 169-183. http://dx.doi.org/10.4137/CMT.S7266

[11] Lawrence, R.S. (2007) Disorders of Cobalamin (Vitamin B_{12}) Metabolism: Emerging Concepts in Pathophysiology, Diagnosis and Treatment. *Blood Reviews*, **21**, 113-130. http://dx.doi.org/10.1016/j.blre.2006.05.001

[12] Reynolds, E. (2006) Vitamin B_{12}, Folic Acid, and the Nervous System. *The Lancet Neurology*, **5**, 949-960. http://dx.doi.org/10.1016/S1474-4422(06)70598-1

[13] Beltramo, E., Berrone, E., Tarallo, S. and Porta, M. (2008) Effects of Thiamine and Benfotiamine on Intracellular Glucose Metabolism and Relevance in the Prevention of Diabetic Complications. *Acta Diabetologica*, **45**, 131-141. http://dx.doi.org/10.1007/s00592-008-0042-y

[14] Stracke, H., Gaus, W., Achenbach, U., Federlin, K. and Bretzel, R. (2008) Benfotiamine in Diabetic Polyneuropathy (BENDIP): Results of a Randomised, Double Blind, Placebo-Controlled Clinical Study. *Experimental and Clinical Endocrinology and Diabetes*, **116**, 600-605. http://dx.doi.org/10.1055/s-2008-1065351

[15] Maebashi, M., Makino, Y., Furukawa, Y., Kosaku, O., Kimura, S. and Sato, T. (1993) Therapeutic Evaluation of the Effect of Biotin on Hyperglycemia in Patients with Non-Insulin Dependent Diabetes Mellitus. *Journal of Clinical Biochemistry and Nutrition*, **14**, 211-218. http://dx.doi.org/10.3164/jcbn.14.211

[16] Packer, L., Tritschler, H.J. and Wessel, K. (1997) Neuroprotection by the Metabolic Antioxidant α-Lipoic Acid. *Free Radical Biology & Medicine*, **22**, 359-378. http://dx.doi.org/10.1016/S0891-5849(96)00269-9

[17] Azhary, H., Farooq, M.U., Bhanushali, M., Majid, A. and Kassab, M.Y. (2010) Peripheral Neuropathy: Differential Diagnosis and Management. *American Family Physician*, **81**, 887-892.

[18] Kathleen, A. (2006) Peripheral Neuropathy: Pathogenic Mechanisms and Alternative Therapies. *Alternative Medicine Review*, **11**, 294-329.

[19] Maladkar, M., Saggu, N., Moralwar, P., Mhate, A.A., Zemse, D. and Bhoraskar, A. (2013) Evaluation of Efficacy and Safety of Epalrestat and Epalrestat in Combination with Methylcobalamin in Patients with Diabetic Neuropathy in a

Randomized, Comparative Trial. *Journal of Diabetes Mellitus*, **3**, 22-26. http://dx.doi.org/10.4236/jdm.2013.31004

[20] Maladkar, M., Rajadhyaksha, G., Venkataswamy, N., Hariharan, R.S. and Lohati, S.R. (2009) Efficacy, Safety, and Tolerability of Epalrestat Compared to Methylcobalamine in Patients with Diabetic Neuropathy. *International Journal of Diabetes in Developing Countries*, **29**, 28-34. http://dx.doi.org/10.4103/0973-3930.50712

[21] Maladkar, M., Srividya, S. and Parmi, P. (2013) Post-Marketing Surveillance of Epalrestat and Methylcobalamin—Game Changer in the Management of Diabetic Neuropathy: An Indian Perspective. *The Indian Practitioner*, **66**, 683-688.

[22] World Health Organization (2006) Neurological Disorders: Public Health Challenges. World Health Organization, 111-174. http://www.WHOwhqlibdoc.who.int/trs/WHO_TRS_654_(part2).pdf

[23] Kumar, N. (2007) Nutritional Neuropathies. *Neurologic Clinics*, **25**, 209-255. http://dx.doi.org/10.1016/j.ncl.2006.11.001

[24] Luo, J.J., Sivaraaman, K., Nouh, A. and Dun, N.J. (2014) Elevated Plasma Level of Homocysteine Is an Independent Risk Factor for Peripheral Neuropathy. *British Journal of Medicine & Medical Research*, **4**, 161-169.

[25] Areti, A., Yerra, V.G., Naidu, V.G.M. and Kumar, A. (2014) Oxidative Stress and Nerve Damage: Role in Chemotherapy Induced Peripheral Neuropathy. *Redox Biology*, **2**, 289-295. http://dx.doi.org/10.1016/j.redox.2014.01.006

[26] Bell, D.S. (2010) Metformin-Induced Vitamin B12 Deficiency Presenting as a Peripheral Neuropathy. *Southern Medical Journal*, **103**, 265-267. http://dx.doi.org/10.1097/SMJ.0b013e3181ce0e4d

[27] Steichen, O., Martinez-Almoyna, L. and De Broucker, T. (2006) Isoniazid Induced Neuropathy: Consider Prevention. *Revue des Maladies Respiratoires*, **23**, 157-160. http://dx.doi.org/10.1016/S0761-8425(06)71480-2

[28] Ito, T. and Jensen, R.T. (2010) Association of Long-Term Proton Pump Inhibitor Therapy with Bone Fractures and Effects on Absorption of Calcium, Vitamin B_{12}, Iron, and Magnesium. *Current Gastroenterology Reports*, **12**, 448-457. http://dx.doi.org/10.1007/s11894-010-0141-0

[29] Mintzer, S., Skidmore, C.T. and Sperling, M.R. (2012) B-Vitamin Deficiency in Patients Treated with Antiepileptic Drugs. *Epilepsy & Behavior*: *E & B*, **24**, 341-344.

[30] Zhang, M., Han, W.J., Hu, S.J. and Xu, H. (2013) Methylcobalamin: A Potential Vitamin of Pain Killer. *Neural Plasticity*, **2013**, Article ID: 424651. http://dx.doi.org/10.1155/2013/424651

[31] Sun, Y., Lai, M.S. and Lu, C.J. (2005) Effectiveness of Vitamin B12 on Diabetic Neuropathy: Systematic Review of Clinical Controlled Trials. *Acta Neurologica Taiwanica*, **14**, 48-54.

[32] Stracke, H., Lindemann, A. and Federlin, K. (1996) A Benfotiamine-Vitamin B Combination in Treatment of Diabetic Polyneuropathy. *Experimental and Clinical Endocrinology & Diabetes*, **104**, 311-316. http://dx.doi.org/10.1055/s-0029-1211460

[33] Reljanovic, M., Reichel, G., Rett, K., Lobisch, M., Schuette, K., Möller, W., Tritschler, H.J. and Mehnert, H. (1999) Treatment of Diabetic Polyneuropathy with the Antioxidant Thioctic Acid (α-Lipoic Acid): A Two Year Multicenter Randomized Double-Blind Placebo-Controlled Trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy. *Free Radical Research*, **31**, 171-179. http://dx.doi.org/10.1080/10715769900300721

[34] Ziegler, D., Ametov, A., Barinov, A., Dyck, P.J., Gurieva, I., Low, P.A., Munzel, U., Yakhno, N., Raz, I., Novosadova, M., Maus, J. and Samigullin, R. (2006) Oral Treatment with α-Lipoic Acid Improves Symptomatic Diabetic Polyneuropathy: The SYDNEY 2 Trial. *Diabetes Care*, **29**, 2365-2370. http://dx.doi.org/10.2337/dc06-1216

[35] Parry, T.E. (1994) Folate Responsive Neuropathy. *Presse Médicale*, **23**, 131-137.

[36] Yatzidis, H., Koutsicos, D., Agroyannis, B., Papastephanidis, C., Francos-Plemenos, M. and Delatola, Z. (1984) Biotin in the Management of Uremic Neurologic Disorders. *Nephron*, **36**, 183-186. http://dx.doi.org/10.1159/000183149

[37] Koutsikos, D., Agroyannis, B. and Tzanatos-Exarchou, H. (1990) Biotin for Diabetic Peripheral Neuropathy. *Biomedicine & Pharmacotherapy*, **44**, 511-514. http://dx.doi.org/10.1016/0753-3322(90)90171-5