



A Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy of a Nerve Support Formula on Neuropathic Pain in Individuals Suffering from Type II Diabetes Mellitus

William Cross ¹, Shalini Srivastava ²

¹Research and Development, Vasocorp, Hiram, GA, USA; ²Clinical Development, Vedic Lifesciences, Thane, India

Correspondence: Dr Shalini Srivastava, 118, Morya House, Opp. Infinity Mall, Andheri (West), Mumbai, 400053, Maharashtra, India, Email shalini.s@vediclifesciences.com

Background: The primary objective of the present study was to evaluate the effects of a Nerve Support Formula NeuropAWAY[®] on diabetic neuropathic pain.

Methods: This double-blind, placebo-controlled, randomized trial was conducted between August 2020 and February 2021. Patients aged ≥ 40 and ≤ 65 years with a history of type 2 diabetes (T2D) with a confirmed diagnosis of diabetic neuropathic pain were included in the study. The primary efficacy endpoint was to assess the effect of the 42 days administration of the Nerve Support Formula on the neuropathic pain as assessed by the 11 point Pain Intensity Numeric Rating Scale (PI-NRS). The secondary objectives were to assess the effect on plasma vitamin B12 levels, nerve conduction velocity, blood flow velocity, Brief Pain Inventory, Neuropathy Total Symptom Score, and Insomnia Severity Index.

Results: The enrolled study population (n=59) was randomized in two study groups; the Investigational Product (IP) group - Nerve Support Formula (n=27) and placebo group (n=32). The mean age of these participants was 52.63 and 53.72 for IP and placebo group, respectively. The mean (SD) HbA1c levels for IP and placebo group were 8.37 (0.85) and 8.16 (0.86), respectively. By the end of the study (Day 42) the decrease in PI-NRS scores for the IP group was maximal ($\downarrow 61.32\%$) and highly significant ($p < 0.001$) in comparison to the placebo group ($\uparrow 2.47\%$). Significant improvements ($p < 0.05$) were also noted in the secondary efficacy variables after 42 days of IP intake.

Conclusion: The formula was found to be significantly effective as compared to placebo in reducing pain and other sensory symptoms related to the diabetic peripheral neuropathy.

Keywords: diabetes mellitus, neuropathic pain, supplements, vitamin B12, placebo controlled

Introduction

Diabetes Mellitus is a rising healthcare condition that now affects over 451 million people worldwide,¹ with the number predicted to rise to 693 million by 2045.² Diabetic peripheral neuropathy (dPN) is the most frequent of the typical medical consequences, and it is associated with increased morbidity and death. It is defined as a unique type of neurodegeneration that occurs in the peripheral nervous system, which impairs nerve function by targeting the sensory, autonomic, and motor axons.³⁻⁵ Over time, at least 50% of people with T2D will acquire dPN at some point in their lives.⁶ It is a result of nerve damage and is produced by a combination of metabolic, autoimmune, neurovascular, lifestyle, mechanical nerve injury, hereditary characteristics, and other factors. Furthermore, dPN is the major cause of disability in people with T2D, owing to its consequences, which include autonomic abnormalities and diabetic foot events. Painful diabetic neuropathy not only deteriorates quality of life, affects sleep and recreation, disrupts mental well-being, causes melancholy, ataxia, and anxiety, but it's also linked to noncompliance with treatment.⁷ According to the findings, neuropathic pain has a higher psychological cost than nociceptive pain and is also regarded to be more severe than other forms of pain. Significant pain alleviation has been shown to significantly

enhance quality-of-life indicators, such as sleep patterns and overall well-being. Known analgesic medications, such as non-steroidal anti-inflammatory medicines (NSAIDs) and opiates,^{8–10} are commonly used to treat neuropathic pain associated with dPN. As reported in a meta-analysis,¹¹ most of the pharmacological treatments have limited efficacy with an effect size as small as <0.5. This concern drew the attention of the medical fraternity towards nutraceuticals and other nonpharmaceutical supplements that may serve to work in synergy with existing pharmaceutical-based treatment regimens for combatting chronic neuropathic pain. The antioxidant, anti-inflammatory, anti-apoptotic, neuroprotective, and calcium inhibitory activities of supplemental vitamins and amino acids have demonstrated significant analgesic effects.¹² People withstanding long-term diabetes mellitus often present with vitamin B12 deficiency, thereby triggering peripheral neuropathy.¹³ Methylcobalamin (MeCbl) is known to have a neuroprotective role by aiding in the synthesis of neuronal lipids as well as regeneration of axonal nerves.^{14,15} A study has reported a decrease in the pain score in the dPN individuals post-consumption of Vitamin B12 as it further activates the MeCbl mediated methylation.¹⁶ MeCbl has been proven efficacious for treatment of dPN, when it is amalgamated with other amino acids. A meta-analysis compared the effect of the MeCbl alone to that when it was combined with lipoic acid on diabetic peripheral neuropathy. The results indicated that, compared to MeCbl alone, the combination with lipoic acid resulted in a better outcome for the neuropathic symptoms.¹⁷

Furthermore, it is already established that sorbitol accumulation in the nerve is responsible for the progression of diabetic peripheral neuropathy. Excessive levels of intracellular glucose get metabolized to sorbitol through aldose reductase. In response to this change in osmolality, levels of organic osmolytes, including sorbitol, taurine, and myo-inositol, get depleted. Stevens conducted a study where aldose reductase inhibitor was administered into STZ-treated diabetic rats who were taurine deficient. As a result, it attenuated the depletion of taurine.¹⁸ This observation suggests that taurine is an essential metabolite for nerve function. Another study observed diabetic neuropathy in a STZ-treated diabetic model post-aurine supplementation. It reported that the defective nerve functions were improved, such as nerve conductance deficits and hyperalgesia, and ameliorated the deficit of nerve blood flow.^{19–21} Additionally, taurine supplementation has been found to be more useful against diabetic peripheral neuropathy. Another study observed improvement in dPN associated deficits of hind limb sciatic motor and digital sensory nerve conduction velocity, nerve blood flow, and sensory thresholds.⁸

Acetyl-L-carnitine (ALC) is found to be deficient in diabetic individuals.^{22,23} Its role in the treatment of dPN is uncertain. Existing research indicates that carnitine increases the blood concentration of unbound carnitine. Preclinical studies have demonstrated that substitution with ALC corrects perturbations of neural Na⁺/K⁺-ATPase, myo-inositol, nitric oxide (NO), prostaglandins, and lipid peroxidation, all of which play important early pathogenetic roles in dPN.^{24,25} Clinical studies have shown that ALC is efficacious in the treatment of painful neuropathies.^{26,27}

Oral L-arginine supplementation has been used in several studies to improve endothelium-dependent, nitric oxide (NO)-mediated vasodilation. Evidently it had a drawback of extensive presystemic elimination due to intestinal arginase activity. In contrast, L-citrulline has been readily absorbed and at least in part converted to L-arginine. It works as an adjuvant in raising the l-arginine plasma concentrations in healthy humans. After 1 week of oral supplementation, 0.75 g of l-citrulline twice daily increased C_{max} for plasma l-arginine and AUC for plasma l-arginine to the same extent as did l-arginine did. The results suggest that oral l-citrulline is effective in improving plasma l-arginine concentrations, which is further beneficial for treatment of dPN.²⁸

Beta alanine (B-ALA), a non-essential amino acid, is shown to increase muscle buffering capacity and decrease muscle fatigue.²⁹ B-ALA supplementation is an effective ergogenic aid when administered on a chronic basis over at least 4 weeks.³⁰ A study reported sensory symptom associated with heat and tingling post B-ALA ingestion.³¹ Thus, it is proposed that B-ALA in the formulation will invoke sensory perception of painful sensations in cases of dPN. A ligand for G-protein coupled receptor TGR7 participates in the modulation of neuropathic pain. Preclinical studies have supported that B-ALA has the potential to drive the pathway.³²

Increased oxidative stress plays a major role among the essential pathogenic mechanisms of diabetic neuropathy.^{33,34} α -lipoic acids is one such antioxidant that has shown its ability in improving experimental diabetic neuropathy.^{35,36} It was introduced in Germany as early as 1959 to treat acute liver poisoning. Based on the results, physicians began to prescribe this for neuropathic complaints.³⁷ Based on the evidence of the mechanistic potential, some attempts have been made to evaluate the efficacy and safety of α -lipoic acid in patients with diabetic polyneuropathy.³⁸

Based on the diversified potential and emerging data on the effectiveness of individual ingredients, the Nerve Support formula (ie, NeuropAWAY[®]) has been formulated to avert the symptoms of painful neuropathy. The present study aimed to evaluate the effect of this formula on pain and other symptoms related to diabetic neuropathy.

Materials and Methods

This double-blind, placebo-controlled, randomized trial was conducted between August 2020 and February 2021. The planned sample size for the present study was screened participants: $n=79$, randomized participants: $n=64$, completed participants: $n=50$ (25 completed research participants per arm considering a 22% dropout rate). The sample size was planned as per a similar study done previously.³⁹ All the included study participants provided a signed informed consent form and the study protocol was approved by the ACEAS – an Independent Ethics Committee (Ahmedabad, Gujarat, India). The study was registered with the clinical trials registry of NIH, “clinicaltrials.gov” bearing NCT No: NCT04504305. This study has been conducted in compliance with recognized international standards, including the International Conference on Harmonization (ICH), and the principles of the Declaration of Helsinki. Primarily males and females aged between 40 to 65 years complaining of lower limb pain were included in the study. Participants reported a history of diabetes mellitus for more than 1 year with a confirmed diagnosis of diabetic neuropathic pain as confirmed by PI-NRS⁴⁰ score ≥ 6 . All the included participants had HbA1c levels ≥ 7.1 and $\leq 9.5\%$, even after currently being on anti-diabetics which compulsorily included metformin. The participants had a score of ≥ 4 on the Neuropathic pain DN4 Questionnaire.⁴¹ Neuropathy assessment was analyzed through CNE criteria,⁴² where sensory tests, muscle strength, and ankle reflexes are assessed on lower limbs. The participants included in this study had a moderate degree of neuropathy as their CNE score was between 10–18. The major exclusion criteria were: severe cardiac disease, uncontrolled hypertension defined as systolic blood pressure ≥ 139 mmHg, and diastolic blood pressure ≥ 85 mmHg, renal insufficiency, history of intermittent claudication, muscular disorders or rheumatoid arthritis, type 2 diabetes mellitus with a history of foot ulcers in the last 6 months prior to the study, history of nerve damage not due to painful diabetic neuropathy, systemic chemotherapy or immunotherapy within the past 5 years, individuals on taurine, citrulline, or other amino acid supplementation, participants who consumed PDE5 inhibitors regularly or periodically, and females who were pregnant or lactating at the time of screening. All the participants were asked to mandatorily abstain from caffeine and alcohol prior to scheduled clinic visits.

The study product is a patented formula containing 240 mcg MeCbl and 1,200 mg of proprietary blend containing taurine, ALC, L-citrulline, B-ALA, and R-alpha-lipoic acid. Stratified block randomization using blocks of 4 was performed using the Stats direct software version 3.1.17. The participants were randomized in two groups: the first group was given IP (800 mg/capsule) and the second group was given placebo (microcrystalline cellulose, 800 mg/capsule). All the participants were advised to take two capsules half an hour prior to meals three times a day, cumulating in a daily dose of 4,800 mg/day. The investigational product was manufactured in a GMP certified facility. In order to preserve the blinding, active and placebo capsules were matched for size, shape, color, and texture. They were packed in HDPE bottles, which were similar in terms of size, color, as well as labeling. The participants were followed-up for 6 weeks (42 days).

The primary objective of the study was to assess the effect of the product on the pain intensity assessed by the change in the pain intensity-numeric rating scale (PI-NRS) score from baseline to the end of the study as compared to the change in the placebo group. The secondary objectives were change in the plasma Vitamin B12 levels, nerve conduction velocity, and lower limb blood flow velocity. The study also assessed the effect of 42 days of the IP administration on the daily functioning due to pain severity using the brief pain inventory and neuropathy sensory symptoms using the NTSS-6 scale.⁴³ As per the recommendation of The European Medicines Agency,⁴⁴ responder analysis was done using BPI score. Participants with a BPI score reduction of $\geq 50\%$ from the baseline score were classified as excellent responders, whereas those with $\geq 30\%$ were considered as moderate responders.

Statistical Analysis

The continuous variables are represented as mean and standard deviation, and the categorical variables are presented as numbers and percentages. All efficacy and the safety endpoints were analyzed for the mITT population. All randomized participants who met all the inclusion/exclusion criteria, administered at least one dose of the IP, and completed at least the Day 14 visit were included in the mITT population. The blinding of the treatment groups was only opened after the analysis

of the data. The summary and analysis of change of designated efficacy and safety parameters for the study were compiled using two sample *t*-test/Mann Whitney *U*-test. The R/SAS9.4/ SPSS Version 10.0 was used for all statistical analysis.

Results

Study Participants

A total of 95 participants were screened and 64 participants fulfilling inclusion/exclusion criteria were randomized in a 1:1 ratio to receive either the IP or placebo. Three participants were excluded from the study post-randomization as they were not satisfying all the specified criteria. Finally, 27 participants were randomized in the IP group and 32 in the placebo group. The detailed presentation of participant's flow is depicted in Figure 1. The mean age (SD) of the participants in the IP group was 52.63 (8.23) years and 53.72 (6.92) years in the placebo group. All included participants were on metformin (1,000 mg/day) compulsorily and the dose and regimen for metformin did not change throughout the study. The participants were also allowed to continue their ongoing antidiabetic treatment with exclusion of insulin. The basic demographic details and medical history of the participants is presented in Table 1; the randomized participants did not show any significant difference between any demographic parameter at baseline (p -value >0.05).

Primary Efficacy

Pain Intensity Numeric Rating Scale (PI-NRS)

The PI-NRS scores have been summarized as by Day 7 ($p=0.0060$), 28 ($p<0.0001$), and day 42 ($p<0.0001$) (Table 2). Consumption of the IP resulted in a significant reduction in PI-NRS after 7 days of consumption from baseline with an absolute change of -0.93 in comparison to placebo (-0.06 , $p<0.0001$) (Figure 2A). A similar trend was observed on days 28 and 42 in the IP group with an absolute change of -3.04 and -4.78 in comparison to placebo (-0.06 , 0.16 ;

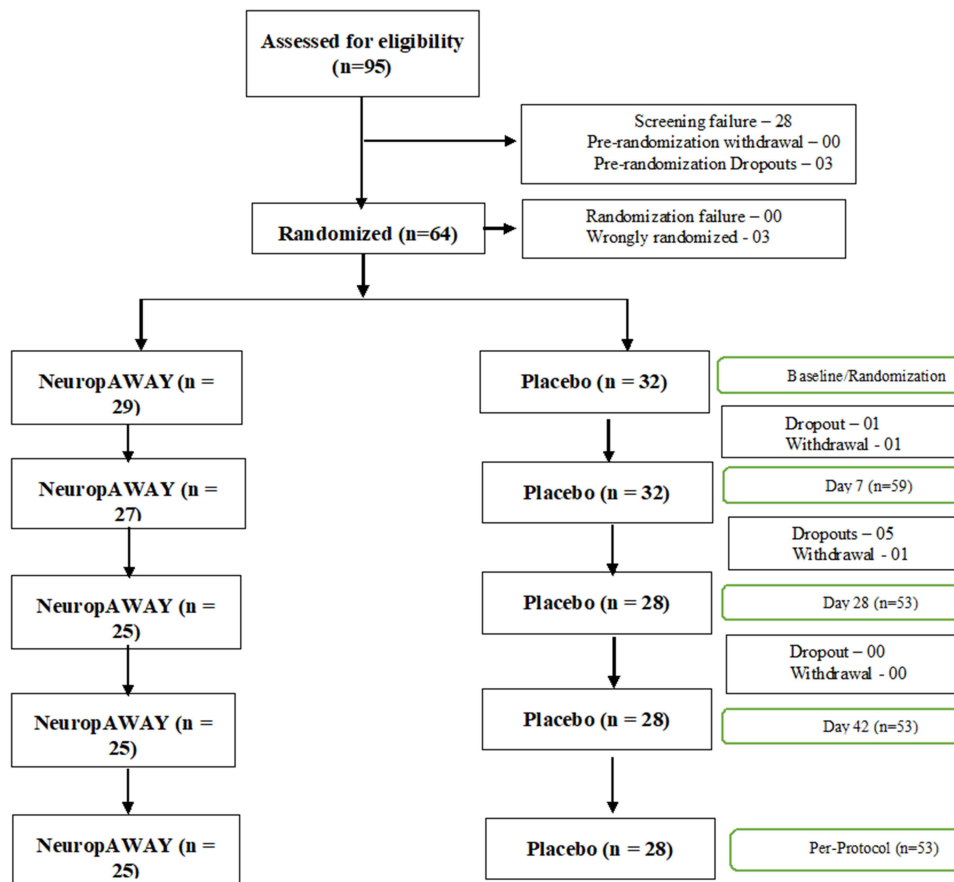


Figure 1 Participant disposition chart.

Table 1 Basic Demographic Details of Participants

Parameters	IP (Mean (SD))	Placebo (Mean (SD))	p-value
N	27	32	–
Age (years)	52.63 (8.23)	53.72 (6.92)	0.78
Weight (Kg)	68.34 (8.14)	70.14 (10.86)	0.48
BMI (Kg/m ²)	27.14 (3.23)	26.80 (3.50)	0.70
Duration of diabetes (years)	8.09 (5.70)	7.95 (6.23)	0.931
Clinical neurological examination (CNE) score	12.59 (4.23)	12.19 (5.41)	0.37
Neuropathic pain diagnostic questionnaire (dPN4)	6.93 (1.14)	6.75 (1.55)	0.52
PI-NRS (Index Limb)	7.81 (0.96)	7.84 (1.08)	0.92
Pulse rate (bpm)	79.93 (4.17)	79.38 (4.78)	0.75
SBP (mm Hg)	125.03 (8.60)	123.66 (7.42)	0.43
DBP (mm Hg)	77.14 (4.21)	78.03 (4.40)	0.30
HbA1c (%)	8.37 (0.85)	8.16 (0.86)	0.30
AST (U/L)	24.59 (8.25)	24.27 (12.63)	0.23
ALT (U/L)	27.37 (16.00)	25.56 (18.17)	0.35
Serum Creatinine (mg/dL)	0.79 (0.27)	0.82 (0.23)	0.55
Gender Distribution, n (%)			
Male	13 (48.15%)	17 (53.13%)	0.93
Female	14 (51.85%)	15 (46.88%)	
Medical History, n (%)			
Hyperacidity, n (%)	1 (3.45%)	0 (0.00%)	
Hypertension, n (%)	11 (37.93%)	16 (50.00%)	

Notes: p-value was calculated using two sample t-test(T)/Mann Whitney-U test(U).

Abbreviations: SD, Standard deviation; n, Number of participants.

Table 2 PI-NRS of the Participants During Study Duration

Treatment [Mean (SD)]	IP (n=27)	p-value [#]	Placebo (n=32)	p-value [#]	p-value [*]
Day 0	7.81 (1.04)		7.88 (1.04)		0.98
Day 7	6.89 (1.37)	<0.0001	7.81 (0.93)	0.6875	0.006
Day 28	4.78 (1.40)	<0.0001	7.81 (1.18)	0.8331	<0.0001
Day 42	3.04 (1.68)	<0.0001	8.03 (1.06)	0.3593	<0.0001

Notes: ^{*}Between-group p-value was calculated using Mann Whitney U-test. [#]Within-group p-value was compared with baseline and calculated using Wilcoxon Signed Rank test (W).

$p < 0.0001$, respectively). The greatest numerical reduction in pain observed in the IP group was on day 42, with an absolute change value of -4.78 . The percent changes in PI-NRS (mITT) at days 7, 28, and 42 are shown graphically in Figure 2B. By the end of the study (Day 42) the percent decrease in PI-NRS scores for the IP group was maximal

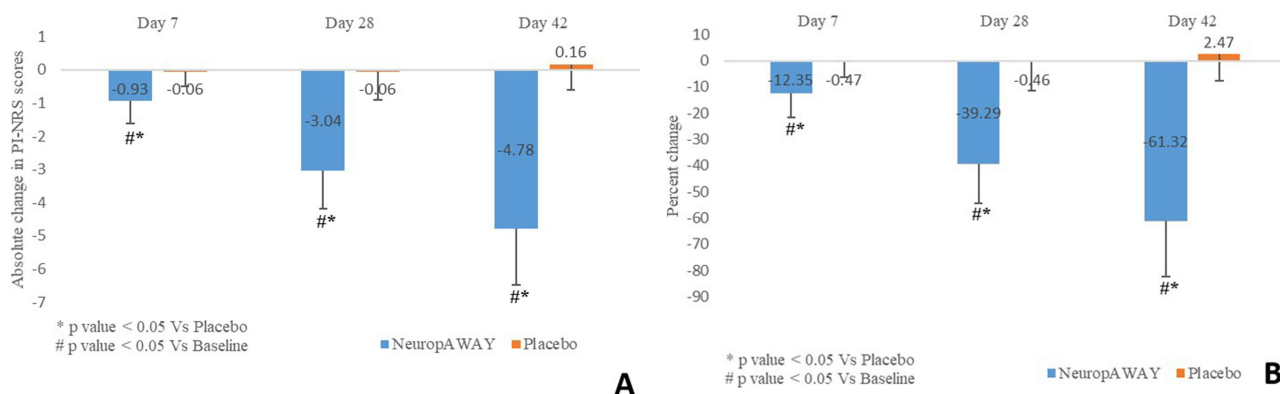


Figure 2 (A) Absolute change in PI-NRS score; **(B)** Percentage change in PI-NRS score.

(↓61.32%) and highly significant ($p < 0.001$) in comparison to the placebo group (↑2.47%). Based on these findings it can be concluded that the consumption of this formula results in a significant reduction in pain, with a progressive reduction in pain over time.

Secondary Efficacy

The study also explored the changes in the Plasma Vitamin B12 levels, 24-hours pain using the Brief Pain Inventory, Neuropathic symptoms using the NTTS-6 scale, sleep quality using the Insomnia Severity Index, nerve conduction by the Nerve Conduction Velocity test, and peripheral blood flow velocity by Doppler.

Plasma Vitamin B12 Levels

Plasma vitamin B12 levels from baseline to the end of treatment were compared to placebo (Table 3). The vitamin B12 levels have been summarized using mean, SD, with the analysis performed based on the mITT population. Both the IP and placebo group presented with Vitamin B12 deficiency at the baseline, which was statistically comparable amongst the group ($p = 0.4225$). Vitamin B12 deficiency in diabetics, is generally a result of the imbalance in the methylation process.²³ After 42 days of study product(s) consumption, the vitamin B12 levels increased to 162.48 pmol/L in the IP group and decreased to 83.80 pmol/L in the placebo group, the intergroup difference on day 42 being statistically significant; $p = 0.0014$.

Intergroup analysis of the per protocol population revealed that consumption of the formula for 42 days resulted in a significant increase of vitamin B12 levels by 93.46% (↑37.62 pmol/L) in comparison to the placebo group where vitamin B12 levels decreased by -3.01% (↓14.35 pmol/L). Within-group analysis revealed that the increase in vitamin B12 levels in IP group on day 42 from baseline was statistically significant ($p = 0.0003$).

Based on the above findings, it can be concluded that consumption of the IP for 42 days' results in a significant increase in the serum levels of active vitamin B12, which may halt the progression of the disease by decreasing the rate of neurodegeneration and thereby may help in alleviating the clinical symptoms of dPN.

Brief Pain Inventory (BPI)

Pain severity from baseline to the end of treatment in comparison to placebo was assessed by weekly score for 24-hours pain severity using the Brief Pain Inventory (BPI) (Table 3). Total BPI score was utilized for investigating the percentage of responders. Clinical response was defined in two parts, moderate and excellent response. Moderate response to the treatment was defined by a 30% improvement experienced by the participant at the end of the treatment period as compared to baseline, assessed as per BPI severity index total score. Similarly, an excellent response was defined as a 50% improvement experienced by the participant at the end of the treatment period, as compared to baseline, in BPI severity index total score.

On day 7, out of 59 participants, the percentage of responders (moderate) was higher in the IP group when compared to the placebo group (3.70% vs 0.00%); however, the difference was not statistically significant; $p = 0.4576$. A similar

Table 3 Details of Secondary Objectives at Baseline and Day 42

Variables (Mean (SD))	IP (n=27)			Placebo (n=32)			P-value
	Day 0	Day 42	Change	Day 0	Day 42	Change	
Vit B12	131.43 (94.80)	162.48 (88.99)	37.62 (54.87)	103.22 (78.50)	83.80 (54.25)	-14.35 (52.69)	0.001
Brief Pain Inventory	6.01 (0.90)	2.55 (1.34)	-3.46 (1.55)	5.84 (0.98)	6.05 (1.05)	0.21 (0.42)	<0.0001
Moderate Treatment Response, n (%)	–	25 (92.59%)	–	–	0 (0.00%)	–	<0.0001
Excellent Treatment Response, n (%)	–	23 (85.19%)	–	–	0 (0.00%)	–	<0.0001
NTTS-6	10.44 (3.22)	3.34 (2.17)	-7.22 (2.37)	10.11 (3.80)	10.99 (4.05)	0.81 (0.85)	<0.0001
Insomnia Severity Index	12.85 (5.50)	4.48 (2.67)	-8.37 (5.38)	12.63 (4.04)	13.84 (4.65)	1.22 (2.39)	<0.0001
Nerve Conduction Velocity Test (m/s)							
Ankle Peroneal Amp (mV)	5.31 (3.59)	5.35 (2.52)	0.17 (2.27)	5.09 (2.93)	5.18 (3.06)	0.33 (1.13)	0.85
Ankle Tibial Amp (mV)	9.63 (5.74)	10.56 (5.63)	0.67 (1.86)	9.63 (5.71)	10.09 (6.31)	0.20 (2.62)	0.78
Knee Peroneal Amp (mV)	4.37 (2.79)	4.36 (1.72)	0.07 (1.97)	4.16 (2.30)	4.20 (2.55)	0.29 (1.51)	0.97
Knee Tibial Amp (mV)	7.30 (4.61)	7.66 (4.16)	0.04 (1.77)	6.61 (3.91)	7.41 (4.51)	0.66 (1.95)	0.83
Ankle Peroneal NCV (m/s)	45.94 (5.67)	45.44 (5.29)	-0.89 (4.28)	42.70 (4.89)	43.99 (3.81)	0.62 (4.74)	0.26
Ankle Tibial NCV (m/s)	41.89 (5.34)	42.79 (3.88)	0.28 (3.53)	40.85 (5.66)	42.65 (5.64)	1.02 (4.96)	0.95
Sural NCV (m/s)	53.81 (8.58)	55.17 (8.84)	2.01 (10.09)	50.68 (6.36)	53.70 (7.78)	4.24 (8.11)	0.50
Blood flow velocity – Femoral artery (cm/sec)							
Right common	95.11 (24.26)	93.32 (30.23)	-2.10 (29.21)	94.45 (35.24)	92.89 (36.92)	-3.29 (30.71)	0.85
Left common	90.44 (26.88)	95.08 (35.20)	2.99 (27.98)	90.29 (30.46)	92.98 (32.10)	3.41 (21.83)	0.87
Proximal right superficial	73.52 (16.69)	73.72 (17.08)	0.44 (16.12)	74.17 (21.59)	79.06 (21.79)	2.57 (17.13)	0.32
Proximal left superficial	69.91 (18.44)	74.60 (18.85)	3.70 (18.25)	78.22 (22.62)	78.31 (21.81)	-0.50 (17.40)	0.51
Mid right superficial	69.60 (20.34)	66.42 (17.59)	-0.85 (-1.40)	71.14 (21.53)	71.72 (19.39)	0.33 (18.74)	0.26
Mid left superficial	64.98 (16.13)	66.41 (21.38)	2.70 (18.12)	69.89 (20.86)	65.98 (20.46)	-4.59 (12.05)	0.85
Distal right superficial	60.17 (20.21)	61.38 (16.61)	1.84 (15.45)	65.94 (25.23)	68.08 (19.17)	-0.34 (21.75)	0.18
Distal left superficial	56.50 (16.34)	53.52 (13.76)	-1.84 (17.46)	62.46 (23.22)	62.75 (19.60)	-1.36 (19.13)	0.06

Notes: p-value was calculated using two sample t-test (T)/Mann Whitney-U test (U).

Abbreviations: SD, Standard deviation; n, Number of participants.

trend was observed on day 14, where the percentage of responders (moderate) was comparatively higher in the IP group when compared to placebo (11.11% vs 0.00%; $p=0.09$). Noticeably, after 21 days of IP consumption, the % of moderate responders was significantly higher when compared to placebo (44.44% vs 0.00%; $p<0.0001$), and this incremental trend was consistent even after 28 (74.07% vs 0.00%; $p<0.0001$), 35 (85.19% vs 0.00%; $p<0.0001$), and 42 (92.59% vs 0.00%; $p<0.0001$) days of supplementation.

In regards to excellent responders, no such responders were observed in any of the study arms till day 14. On day 21, 7.41% of the study participants in the IP arm responded excellently, whereas in the placebo group no such responders were identified (0.00%). However, this comparison was not statistically significant ($p=0.2051$). The percentage of excellent responders kept on increasing significantly in the IP group when compared to placebo after 28 (22.22% vs 0.00%; $p=0.0066$), 35 (48.15% vs 0.00%; $p<0.0001$) and 42 (85.19% vs 0.00%; $p<0.0001$) days of study product(s) consumption. The maximum number of responders was identified in the IP group on day 42 (Moderate =92.59%,

Excellent =85.19%) whereas no responders were identified in the placebo group (Moderate =0.00%, Excellent =0.00%) throughout the treatment period.

Neuropathy Total Symptom Score 6 Questionnaires (NTSS-6)

For the NTSS-6, the six subdomains that have been analyzed are; 1) Numbness, 2) Prickling and Tingling, 3) Burning sensation, 4) Aching pain and tightness, 5) Sharp, shooting, lancinating pain, and 6) Allodynia and Hyperalgesia. On the baseline visit, all six subdomain scores, as well as the total scores, were comparable between the IP and placebo arms; $p>0.05$, which later got reduced significantly by the end of the study (Day 42); $p<0.05$.

Intergroup analysis revealed that supplementation with the IP for 42 days resulted in a significant reduction in all the subdomain scores in comparison to placebo; Numbness (-54.74% vs 8.97%; $p<0.0001$), Prickling and Tingling (-66.00% vs 10.94%; $p<0.001$), Burning sensation (-72.97% vs 5.95%; $p<0.001$), Aching pain and tightness (-76.47% vs 1.43%; $p<0.0001$), Sharp, shooting, lancinating pain (-69.11% vs 13.91%; $p<0.0001$), and Allodynia and Hyperalgesia (-72.27% vs 21.35%; $p<0.0001$), respectively. The same was reflected in NTSS-6 total scores, which significantly reduced by day 42 from baseline in the IP group (69.41%, -7.22) when compared to an increase in the placebo group (8.65%, 0.81; $p<0.0001$) (Table 3). Amongst all the six subdomains, the maximum improvement observed was for aching pain and feeling of tightness domain in the IP group, depicted by a mean percentage reduction of -76.47% from baseline. Within-group analysis showed that the IP consumption resulted in a significant reduction in all six subdomain scores as well as the total scores when compared from baseline; $p<0.0001$.

Insomnia Severity Index

The sleep quality from baseline to the end of treatment in comparison to placebo was assessed by the Insomnia Severity Index (ISI). The mean baseline ISI value of the IP group was comparable with the placebo group, with no statistically significant difference ($p=0.8560$). Intergroup analysis revealed that the IP administration resulted in a significant reduction in ISI scores on day 7 (-2.75%), whereas in the placebo group the ISI scores increased by 2.58%; $p=0.0213$. After 28 days of IP consumption the ISI scores decreased significantly by 40.61% (-5.63) in comparison to placebo, where the sleep quality of the participants deteriorated, as proven by the increase in ISI scores by 6.98% (0.88; $p<0.0001$). More robust improvement was observed after 42 days of supplementation with the Nerve Support formula, as depicted by the reduction in ISI by 60.07% (-8.37) from baseline, whereas in the placebo arm the ISI score increased by 9.99% (1.22; $p<0.0001$) (Table 3).

Within-group analysis revealed that the IP consumption resulted in a significant reduction in ISI scores after 28 and 42 days of supplementation when compared to baseline; $p<0.0001$. Findings demonstrate that IP starts improving the sleep quality after 7 days of supplementation, but more significant improvement can be achieved with a longer duration of supplementation.

Nerve Conduction Velocity and Blood Flow Velocity

Although promising trends were observed, both of these parameters did not show statistically significant results by day 42 (Table 3). These are long-term parameters that may be better studied during a clinical trial of 6 months or longer.

Safety Analysis

The groups matched for their baseline CBC (Haemoglobin (Hb), WBC, Platelets, and absolute Neutrophils count), AST, ALT, and serum creatinine ($p>0.05$). At the end of the study, no statistically significant or clinically relevant changes were observed in any of the stated parameters, demonstrating the good safety profile of the study products (Table 4). No adverse events were reported throughout the study period.

Table 4 Details of Safety Profile at Baseline and Day 42

Parameters	IP (N=29)		Placebo (N=32)		p-value
	Day 0	Day 42	Day 0	Day 42	
WBC (/cmm)	8,922.41 (1,550.67)	8,306.40 (2,090.61)	8,724.56 (2,522.17)	8,290.36 (2,271.87)	>0.05
Platelets (/cmm)	287,206.9 (78,333.71)	281,000.0 (79,057.47)	296,187.5 (90,146.99)	276,785.7 (78,472.15)	
Absolute Neutrophils (/cmm)	5,317.58 (1,333.37)	4,906.41 (1,454.14)	5,372.33 (2,049.03)	5,026.26 (1,644.50)	
AST (U/L)	23.60 (8.77)	23.09 (13.88)	24.27 (12.63)	22.19 (10.58)	
ALT (U/L)	26.17 (16.06)	27.32 (17.12)	25.56 (18.17)	25.07 (16.53)	
Serum Creatinine (mg/dL)	0.83 (0.29)	0.80 (0.23)	0.82 (0.23)	0.81 (0.22)	
HB (mg/dL)	13.27 (1.64)	13.08 (1.48)	13.18 (1.61)	13.05 (1.27)	

Notes: p-value was calculated using two sample t-test (T)/Mann Whitney-U test (U).

Abbreviations: SD, Standard deviation; n, Number of participants.

Discussion

Painful diabetic neuropathy is a serious health concern that affects the quality-of-life and hampers routine activities.⁴⁵ This demands to have a treatment that can relieve the pain and also attenuate the symptoms. However, a variety of drugs are used clinically, alone, or in combination with other agents for dPN. There is none which is determined to be the best in the class. Hence this study has been conducted to fill in the gaps.

We propose that the synergistic effect of MeCbl along with other ingredients are possibly responsible for the significance reported in the study. It is being reasoned based on it's potential to improve the painful conditions in individuals suffering from neuropathic pain, as observed in this study. Research has also indicated the ability of MeCbl in combination form for handling the symptoms of pain.⁴⁶⁻⁴⁸ A 2-week intervention of MeCbl in conjunction with alpha-lipoic acid was conducted which showed an enhanced efficacy in improving the signs of dPN.⁴⁹ Another study documented that MeCbl with pregabalin and with duloxetine were more effective in relieving the painful dPN than MeCbl alone.⁵⁰

Therefore, the effectiveness of a natural supplement which is a blend of MeCbl, taurine, ALC, L-citrulline, B-ALA, and R-alpha-lipoic acid, has been chosen for this study as a Nerve Support Formula for the participants with dPN. The components in this blend have evidence of inducing neuroprotective and neurotrophic effects in the peripheral nervous system.^{51,52} This characteristic is efficacious in reducing the difficulties associated with dPN in people with T2D, the same was intended to be investigated in this study.

Pain was chosen as the primary endpoint of the study as it is the most prevalent clinical symptom of dPN. Administration of IP resulted in a substantial reduction in neuropathic pain after just 7 days of supplementation (-0.93 vs -0.06 , respectively; p -value 0.0001). This downward trend continued until the end of the study, and more robust results were obtained with a longer duration of use, as evidenced by a reduction in PI-NRS by -39.29% (-3.04) and -61.32% (-4.78) in the IP group on days 28 and 42, respectively, which was significantly higher than the placebo group, where PI-NRS scores decreased by -0.46% (-0.06 ; p 0.0001) on day 28. In a study involving Gabapentinoids (GPN),⁵³ the trial product was given in various dosages for nearly 20 weeks. After 20 weeks of GPN treatment at a dose of 1,200 mg/day, the highest numerical drop in mean PI-NRS scores was found to be 2.55. Even at the maximum dose (3,600 mg/day), no significant improvement was found (-2.54). The IP group, on the other hand, showed a maximum numerical drop in mean PI-NRS scores of -4.78 after 42 days of use, which was clearly greater than GPN. Another systematic review and meta-analysis done to evaluate the analgesic effect of gabapentinoids concluded that "no clinically significant analgesic effect for the perioperative use of gabapentinoids was observed".⁵⁴ Another study⁵⁵ evaluating the efficacy of alpha-lipoic acid in a dose of 800 mg/day for 2 months reported a significant decrease in NRS score from baseline, while the placebo group did not show any significant change.

The BPI findings were consistent with the PI-NRS findings, indicating effectiveness of the IP in reducing dPN-related pain and its impairment with daily activities. In addition, the BPI pain intensity index was used to determine who would respond to the treatment. The clinical response was divided into two categories: moderate and excellent. A moderate response to treatment was defined as a 30% improvement, while an excellent response was defined as a 50% improvement from baseline, as measured by the BPI pain severity index total scores at the end of the treatment period. It was discovered that the percentage of responders in the IP group began to increase exponentially. A study by Agathos et al⁵⁶ evaluating the effects of alpha-lipoic acid in participants with painful diabetic neuropathy reported a significant reduction in pain severity as assessed by BPI scores after 40-day consumption of 600 mg alpha-lipoic acid/day.

A number of studies have found an inverse correlation between diabetic neuropathy and vitamin B12 levels in the blood.^{57,58} It may be concluded that supplementing with the nerve support formula for 6 weeks causes a considerable rise in active vitamin B12 levels, which may slow the course of dPN and vitamin B12 deficiency-related neurodegeneration.

Diabetic nerve injury causes aberrant action potential amplitudes and nerve conduction velocities (NCV), as is well documented.⁵⁹ The IP intake did not result in any substantial improvement in NCV or action potential amplitude from baseline or in comparison to placebo at the end of the study. A study investigating the efficacy of Superoxide Dismutase, Alpha Lipoic Acid, Acetyl L-Carnitine, and Vitamin B12 (B12) in one tablet in diabetic neuropathy⁶⁰ reported that at 12-month follow-up the sural nerve conduction action potential and conduction velocity improved significantly. However, the present study was limited to 42 days only and a longer treatment duration is needed to visualize any significant change.

The interventional potential of IP was not demonstrated at a molecular level in this study, which might be attributed to the short treatment time; hence, more research with a longer treatment period is warranted. After 6 weeks of supplementation, a significant reduction in all six symptom scores from baseline was observed in the IP arm in comparison to placebo. The NTSS-6 evaluation showed that the nerve support formula had the ability to manage the principal dPN-related symptoms.

Conclusion

The clinical efficacy and tolerability demonstrated during this 6-week study strongly suggest that this nerve support formula is a suitable candidate for the treatment and management of neuropathic pain and its related complications in patients suffering from diabetic neuropathy.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available upon reasonable request from the authors.

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Disclosure

Mr William Cross reports a patent 11040022. The authors report no other conflicts of interest in this work.

References

1. Hossain P, Kavar B, El Nahas M. Obesity and diabetes in the developing world—a growing challenge. *N Engl J Med*. 2007;356(3):213–215. doi:10.1056/NEJMp068177
2. Cho N, Shaw J, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract*. 2018;138:271–281. doi:10.1016/j.diabres.2018.02.023
3. Yu OHY, Suissa S. Identifying causes for excess mortality in patients with diabetes: closer but not there yet. *Diabetes Care*. 2016;39(11):1851–1853. doi:10.2337/dci16-0026
4. Bertoni AG, Krop JS, Anderson GF, Brancati FL. Diabetes-related morbidity and mortality in a national sample of US elders. *Diabetes Care*. 2002;25(3):471–475. doi:10.2337/diacare.25.3.471
5. Vinik AI, Nevoret M-L, Casellini C, Parson H. Diabetic neuropathy. *Endocrinol Metab Clin*. 2013;42(4):747–787. doi:10.1016/j.ecl.2013.06.001
6. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Primers*. 2019;5(1):1–18. doi:10.1038/s41572-019-0092-1

7. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology*. 2007;68(15):1178–1182. doi:10.1212/01.wnl.0000259085.61898.9e
8. Galuppo M, Giacoppo S, Bramanti P, Mazzon E. Use of natural compounds in the management of diabetic peripheral neuropathy. *Molecules*. 2014;19(3):2877–2895. doi:10.3390/molecules19032877
9. Didangelos T, Veves A. Treatment of diabetic cardiovascular autonomic, peripheral and painful neuropathy. Focus on the treatment of cardiovascular autonomic neuropathy with ACE inhibitors. *Curr Vasc Pharmacol*. 2020;18(2):158–171. doi:10.2174/1570161117666190521101342
10. Iqbal Z, Azmi S, Yadav R, et al. Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. *Clin Ther*. 2018;40(6):828–849. doi:10.1016/j.clinthera.2018.04.001
11. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–173. doi:10.1016/S1474-4422(14)70251-0
12. Forouzanfar F, Hosseinzadeh H. Medicinal herbs in the treatment of neuropathic pain: a review. *Iran J Basic Med Sci*. 2018;21(4):347. doi:10.22038/IJBMS.2018.24026.6021
13. Andrés E, Loukili NH, Noel E, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. *CMAJ*. 2004;171(3):251–259. doi:10.1503/cmaj.1031155
14. Gupta JK, Sana QS. Potential benefits of MeCbl: a review. *Austin J Pharmacol Ther*. 2015;3(3):1076. ISSN: 2373-6208.
15. Kikuchi M, Kashii S, Honda Y, Tamura Y, Kaneda K, Akaike A. Protective effects of MeCbl, a vitamin B12 analog, against glutamate-induced neurotoxicity in retinal cell culture. *Invest Ophthalmol Vis Sci*. 1997;38(5):848–854. PMID: 9112980.
16. Didangelos T, Karlafti E, Kotzakioulafi E, et al. Vitamin B12 supplementation in diabetic neuropathy: a 1-year, randomized, double-blind, placebo-controlled trial. *Nutrients*. 2021;13(2):395. PMID: 33513879; PMCID: PMC7912007. doi:10.3390/nu13020395
17. Xu Q, Pan J, Yu J, et al. Meta-analysis of MeCbl alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy. *Diabetes Res Clin Pract*. 2013;101(2):99–105. doi:10.1016/j.diabres.2013.03.033
18. Stevens MJ, Lattimer SA, Kamijo M, Van Huysen C, Sima AA, Greene DA. Osmotically-induced nerve taurine depletion and the compatible osmolyte hypothesis in experimental diabetic neuropathy in the rat. *Diabetologia*. 1993;36(7):608–614. doi:10.1007/BF00404069
19. Li C, Cao L, Zeng Q, et al. Taurine may prevent diabetic rats from developing cardiomyopathy also by downregulating angiotensin II type2 receptor expression. *Cardiovasc Drugs Ther*. 2005;19(2):105–112. doi:10.1007/s10557-005-0443-x
20. Obrosova IG, Fathallah L, Stevens MJ. Taurine counteracts oxidative stress and nerve growth factor deficit in early experimental diabetic neuropathy. *Exp Neurol*. 2001;172(1):211–219. doi:10.1006/exnr.2001.7789
21. Pop-Busui R, Sullivan KA, Van Huysen C, et al. Depletion of taurine in experimental diabetic neuropathy: implications for nerve metabolic, vascular, and functional deficits. *Exp Neurol*. 2001;168(2):259–272. doi:10.1006/exnr.2000.7591
22. Scarpini E, Doneda P, Pizzul S, et al. L-carnitine and ALCin human nerves from normal and diabetic subjects. *J Peripher Nerv Syst*. 1996;1(2):157–163.
23. Ido Y, McHowat J, Chang KC, et al. Neural dysfunction and metabolic imbalances in diabetic rats: prevention by ALC. *Diabetes*. 1994;43:1469–1477. doi:10.2337/diab.43.12.1469
24. Sima AA, Ristic H, Merry A, et al. The primary preventive and secondary interventional effects of ALC on diabetic neuropathy in the bio-breeding Worcester rat. *J Clin Invest*. 1996;97:1900–1907. doi:10.1172/JCI118621
25. Lowitt S, Malone JJ, Salem AF, Korthals J, Benford S. ALC corrects the altered peripheral nerve function of experimental diabetes. *Metabolism*. 1995;44:677–680. doi:10.1016/0026-0495(95)90128-0
26. Stevens MJ, Lattimer SA, Feldman EL, et al. ALC deficiency as a cause of altered nerve myo-inositol content, Na⁺/K⁺-ATPase activity and motor conduction velocity in the streptozotocin diabetic rat. *Metabolism*. 1996;45:865–872. doi:10.1016/S0026-0495(96)90161-4
27. Scarpini E, Sacilotto G, Baron P, Cusini M, Scarlata G. Effect of ALC in the treatment of painful peripheral neuropathies in HIV+ patients. *J Peripher Nerv Syst*. 1997;2:250–252.
28. Schwedhelm E, Maas R, Freese R, et al. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. *Br J Clin Pharmacol*. 2008;65(1):51–59. PMID: 17662090; PMCID: PMC2291275. doi:10.1111/j.1365-2125.2007.02990.x
29. Stout JR, Cramer JT, Zoeller RF, et al. Effects of beta-alanine supplementation on the onset of neuromuscular fatigue and ventilatory threshold in women. *Amino Acids*. 2007;32:381–386. doi:10.1007/s00726-006-0474-z
30. Stout JR, Cramer JT, Mielke M, O’Kroy J, Torok DJ, Zoeller RF. Effects of twenty-eight days of beta-alanine and creatine monohydrate supplementation on the physical working capacity at neuromuscular fatigue threshold. *J Strength Cond Res*. 2006;20:928–931. doi:10.1519/R-19655.1
31. Harris RC, Tallon MJ, Dunnett M, et al. The absorption of orally supplied beta-alanine and its effect on muscle carnosine synthesis in human vastus lateralis. *Amino Acids*. 2006;30:279–289. doi:10.1007/s00726-006-0299-9
32. Shinohara T, Harada M, Ogi K, et al. Identification of a G protein-coupled receptor specifically responsive to β-alanine. *J Biol Chem*. 2004;279(22):23559–23564. doi:10.1074/jbc.M314240200
33. Low PA, Nickander KK, Tritschler HJ. The roles of oxidative stress and antioxidant treatment in experimental diabetic neuropathy. *Diabetes*. 1997;46:S38–S42. doi:10.2337/diab.46.2.S38
34. Cameron NE, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia*. 2001;44:1973–1988. doi:10.1007/s001250100001
35. Nagamatsu M, Nickander KK, Schmelzer JD, et al. Lipoic acid improves nerve blood flow, reduces oxidative stress and improves distal nerve conduction in experimental diabetic neuropathy. *Diabetes Care*. 1995;18:1160–1167. doi:10.2337/diacare.18.8.1160
36. Cameron NE, Cotter MA, Horrobin DH, Tritschler HJ. Effects of alipoic acid on neurovascular function in diabetic rats: interaction with essential fatty acids. *Diabetologia*. 1998;41:390–399. doi:10.1007/s001250050921
37. Bock E, Schneeweiss J. Ein Beitrag zur Therapie der Neuropathia diabetica. *Munch Med Wochenschr*. 1959;43:1911–1912.
38. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. *Diabet Med*. 2004;21(2):114–121. PMID: 14984445. doi:10.1111/j.1464-5491.2004.01109.x
39. Farvid MS, Homayouni F, Amiri Z, Adelmanesh F. Improving neuropathy scores in type 2 diabetic patients using micronutrients supplementation. *Diabetes Res Clin Pract*. 2011;93(1):86–94. doi:10.1016/j.diabres.2011.03.016
40. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149–158. doi:10.1016/S0304-3959(01)00349-9
41. Spallone V, Morganti R, D’Amato C, Greco C, Cacciotti L, Marfia GA. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. *Diabet Med*. 2012;29(5):578–585. PMID: 22023377. doi:10.1111/j.1464-5491.2011.03500.x

42. Valk GD, Nauta JJ, Strijers RL, Bertelsmann FW. Clinical examination versus neurophysiological examination in the diagnosis of diabetic polyneuropathy. *Diabet Med.* 1992;9(8):716-21. doi:10.1111/j.1464-5491.1992.tb01879.x
43. Kulseng-Hanssen S, Borstad E. The development of a questionnaire to measure the severity of symptoms and the quality of life before and after surgery for stress incontinence. *BJOG.* 2003;110(11):983-988. doi:10.1111/j.1471-0528.2003.01406.x
44. Use CfMPfH. Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus. CPMP/EWP/1080/00 Rev; 2011:1.
45. Kim CH, Jeong SJ, Mok JO, Lee KY, Kim SR. Impact on quality of life in peoples with painful diabetic peripheral neuropathy. In 17th European Congress of Endocrinology; BioScientifica; 2015:EP443.
46. Vasudevan D, Naik MM, Mukaddam QI. Efficacy and safety of MeCbl, alpha lipoic acid and pregabalin combination versus pregabalin monotherapy in improving pain and nerve conduction velocity in type 2 diabetes associated impaired peripheral neuropathic condition. [MAINTAIN]: results of a pilot study. *Ann Indian Acad Neurol.* 2014;17:19. doi:10.4103/0972-2327.128535
47. Prabhoo R, Panghate A, Dewda RP, More B, Prabhoo T, Rana R. Efficacy and tolerability of a fixed dose combination of MeCbl and pregabalin in the management of painful neuropathy. *N Am J Med Sci.* 2012;4:605-607. doi:10.4103/1947-2714.103336
48. Dongre YU, Swami OC. Sustained-release pregabalin with MeCbl in neuropathic pain: an Indian real-life experience. *Int J Gen Med.* 2013;6:413-417. doi:10.2147/IJGM.S45271
49. Han Y, Wang M, Shen J, et al. Differential efficacy of MeCbl and alpha-lipoic acid treatment on symptoms of diabetic peripheral neuropathy. *Minerva Endocrinol.* 2018;43(1):11-18. PMID: 27901334. doi:10.23736/S0391-1977.16.02505-0
50. Sharma C, Kaur I, Singh H, Grover IS, Singh J. A randomized comparative study of MeCbl, MeCbl plus pregabalin and MeCbl plus duloxetine in patients of painful diabetic neuropathy. *Indian J Pharmacol.* 2021;53(5):358-363. PMID: 34854403; PMCID: PMC8641739. doi:10.4103/ijp.ijp_1159_20
51. Rolim LC, da Silva EM, Flumignan RL, Abreu MM, Dib SA. ALCfor the treatment of diabetic peripheral neuropathy. *Cochrane Database Syst Rev.* 2019;6(6):CD011265. PMID: 31201734; PMCID: PMC6953387. doi:10.1002/14651858.CD011265.pub2
52. Shatanawi A, Momani MS, Al-Aqtash R, Hamdan MH, Gharaibeh MN. L-citrulline supplementation increases plasma nitric oxide levels and reduces arginase activity in patients with type 2 diabetes. *Front Pharmacol.* 2020;11:584669. PMID: 33414716; PMCID: PMC7783447. doi:10.3389/fphar.2020.584669
53. Rauck R, Makumi CW, Schwartz S, et al. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. *Pain Pract.* 2013;13(6):485-496. doi:10.1111/papr.12014
54. Verret M, Lauzier F, Zarychanski R, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: a systematic review and meta-analysis. *Anesthesiology.* 2020;133(2):265-279. doi:10.1097/ALN.0000000000003428
55. Esposito C, Garzarella EU, Santarcangelo C, et al. Safety and efficacy of alpha-lipoic acid oral supplementation in the reduction of pain with unknown etiology: a monocentric, randomized, double-blind, placebo-controlled clinical trial. *Biomed Pharmacother.* 2021;144:112308. doi:10.1016/j.biopha.2021.112308
56. Agathos E, Tentolouris A, Eleftheriadou I, et al. Effect of α -lipoic acid on symptoms and quality of life in patients with painful diabetic neuropathy. *J Int Med Res.* 2018;46(5):1779-1790. doi:10.1177/0300060518756540
57. Nexo E, Hoffmann-Lücke E. Holotranscobalamin, a marker of vitamin B-12 status: analytical aspects and clinical utility. *Am J Clin Nutr.* 2011;94(1):359S-65S. doi:10.3945/ajcn.111.013458
58. Alvarez M, Sierra OR, Saavedra G, Moreno S. Vitamin B12 deficiency and diabetic neuropathy in patients taking metformin: a cross-sectional study. *Endocr Connect.* 2019;8(10):1324-1329. doi:10.1530/EC-19-0382
59. Tehrani KHN. A study of nerve conduction velocity in diabetic patients and its relationship with tendon reflexes (T-reflex). *Open Access Maced J Med Sci.* 2018;6(6):1072. doi:10.3889/oamjms.2018.262
60. Didangelos T, Karlafti E, Kotzakioulafi E, et al. Efficacy and safety of the combination of superoxide dismutase, alpha lipoic acid, vitamin B12, and carnitine for 12 months in patients with diabetic neuropathy. *Nutrients.* 2020;12(11):3254. doi:10.3390/nu12113254

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