

## COMPARISON OF THE EFFICACY OF DULOXETINE VERSUS DULOXETINE PLUS ORAL VITAMIN D IN TREATING PERIPHERAL DIABETIC NEUROPATHY

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**Abstract:** Painful diabetic peripheral neuropathy (PDPN) is a common complication of diabetes mellitus that affects the quality of life. Duloxetine and vitamin D have been used for its management, but there is limited literature comparing the efficacy of these drugs. In this study, we aimed to compare Duloxetine alone versus Duloxetine in combination with vitamin D for treating PDPN. An open-labeled randomized controlled trial was conducted at King Edward Medical University, Mayo Hospital, Lahore, for a duration of 6 months, starting from July 1, 2021, to December 31, 2021. The study included 78 patients aged 20 to 60 years suffering from PDPN as per inclusion and exclusion criteria. Participants were randomly assigned to two groups, with 39 participants in each group. Group A was given Duloxetine 60mg OD, and Group B was given Duloxetine 60mg OD plus oral Vitamin D3 2000IU daily for 8 weeks. Patients were assessed before the start of treatment and followed up after 8 weeks in the outpatient department to measure the mean reduction in pain score using the Visual Analogue Scale. All the collected data was analyzed using SPSS 26.0. The mean age of the participants was 44.46 ± 6.51 years. Of the 78 participants, 51 were female, and 27 were male. 89.8% of patients tolerated the drugs well with no side effects. Only 6.4% of patients complained of tiredness, and 3.8% experienced constipation. The mean VAS before treatment and at the end of the 8th week was 7.41 ± 0.98 and 3.48 ± 1.01, respectively. There was a marked reduction in pain after using both regimens, which was statistically significant (p-value < 0.001). The mean VAS before and after the treatment in Group A was 7.46 ± 0.99 and 4.17 ± 0.72, respectively. In Group B, the mean VAS before and after the treatment was 7.35 ± 0.978 and 2.79 ± 0.832, respectively. This reduction was statistically significant compared to the two groups (p-value < 0.001). The combination of Duloxetine and vitamin D proved superior to the Duloxetine group and is a recommended regimen according to our results. Further studies with more extensive data from multiple centers are required to establish the guidelines.

**Keywords:** Diabetic neuropathies, Duloxetine, Vitamin D, Pain management, Randomized controlled trial.

### Introduction

Painful diabetic peripheral neuropathy (PDPN) is a common complication of diabetes mellitus that affects the quality of life. Duloxetine and vitamin D have been used for its management, but there is limited literature comparing the efficacy of these drugs. In this study, we aimed to compare Duloxetine alone versus Duloxetine in combination with vitamin D for treating PDPN. An open-labeled randomized controlled trial was conducted at King Edward Medical University, Mayo Hospital, Lahore, for a duration of 6 months, starting from July 1, 2022, to December 31, 2022. The study included 78 patients aged 20 to 60 years suffering from PDPN as per inclusion and exclusion criteria. Participants were randomly assigned to two groups, with 39 participants in each group. Group A was given Duloxetine 60mg OD, and Group B was given Duloxetine 60mg OD plus oral Vitamin D3 2000IU daily for 8 weeks. Patients were assessed before the start of treatment and followed up after 8 weeks in the outpatient department to measure the mean reduction in pain score using the Visual Analogue Scale. All the collected data was analyzed using SPSS 26.0. The mean age of the participants was 44.46 ± 6.51 years. Of the 78 participants, 51 were female, and 27 were male.

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### Methodology

This was an open-labeled, Randomized Controlled Trial conducted at King Edward Medical University, Mayo Hospital, Lahore, for 6 months from 1<sup>st</sup> July 2021 to 31<sup>st</sup>

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December 2021. A sample size of 78 (39 in each group) patients was calculated by taking a confidence level of 95% and expected mean reduction in VAS score from baseline score in patients treated with Duloxetine 60mg OD as  $3.24 \pm 0.23$  points and Duloxetine 60mg x BD plus Oral Vitamin D3 as  $4.0 \pm 1.2$  points after 8 weeks treatment (Basit et al., 2016; Goldstein et al., 2005).

Diagnosis of PDPN was a diagnosis of exclusion made by ruling out other causes of neuropathy in patients suffering from Diabetes Mellitus (Gomez Gomez, 2021). Diagnosed cases of Diabetes mellitus presenting with symptoms of Painful Diabetic Neuropathy of both genders between age 20 to 60 years were included in the study. Those patients having other complications of Diabetes, like Stroke, which impairs assessment, and critically ill patients were excluded from the study.

All the Diabetic patients with neuropathy obeying inclusion and exclusion criteria were included in this study after obtaining informed consent from them. At the first presentation, all the patients were assessed for pain through a visual analog pain scale (VAS). The visual analog scale is a simple scale in which a line of 10 cm is drawn & one end is marked as 0 (no pain), and the other is marked as 10 (most troublesome pain). The patient is asked to put a line perpendicular to this line according to his perception of pain, and this distance is measured and recorded by a ruler. Demographic variables and brief history were noted on a pre-designed Performa. Patients were randomly divided into two groups, with 39 participants in each group. Group A will be given Duloxetine 60mg OD, and Group B will be given Duloxetine 60mg OD plus oral Vitamin D3 2000IU daily for 8 weeks. Patients will be followed after 8 weeks in the outpatient department for a mean reduction in pain score using VAS. Additionally, any side effect like dry mouth, drowsiness, nausea, anorexia, and constipation was also noted at 8 weeks follow-up to look for the safety and

tolerability of the drugs. The potential side effects and hazards were explained to the patient as well. Treatment compliance and side effects profile were monitored by seeing the record on a diary given to them.

Collected data was analyzed using SPSS 23.0. All baseline characters and variables in history were calculated as Mean and standard deviations for quantitative variables and as percentages for frequencies of qualitative variables like reduction in VAS score. A paired T-test was used to compare both groups' mean reduction in VAS.

## Results

The study included 78 patients (39 in each group). The mean age of the participants was  $44.46 \pm 6.51$  years, and the mean duration of the disease since its diagnosis was  $6.55 \pm 4.04$  years. There were 27 (34.6%) male and 51 (65.4%) female patients. Out of 78, 43 (65.4%) were hypertensive as well. 70 (89.8%) patients tolerated the drugs effectively and reported no side effects. Only 6.4% (5) of patients complained of tiredness, and 3.8% (3) had constipation. The mean VAS before treatment and at the end of the 8<sup>th</sup> week was  $7.41 \pm 0.98$  and  $3.48 \pm 1.01$ . There was a marked reduction in pain after using both regimens, which was statistically significant. (p-value less than 0.001). Compared to the groups, Group A patients who were given Duloxetine alone had a mean age of  $44.58 \pm 6.45$  years, and the mean duration of the disease was  $7.46 \pm 3.42$ . Meanwhile, Group B patients were also given oral Vitamin D3 and Duloxetine. The mean age and duration of the disease in this group were  $44.33 \pm 6.6$  and  $5.64 \pm 4.45$  years, respectively. This is illustrated by the distribution of other variables like gender, Hypertension, and drug side effects in both groups, which are given separately in the table below.

**Table 1. Demographics of the study population**

Variables	Group A	Group B
<b>Age</b>	44.58±6.45	44.33±6.6
<b>Duration</b>	7.46±3.42	5.64±4.45
<b>Gender</b>		
• Male	18(46.2%)	9(23.1%)
• Female	21(53.8%)	30(76.9%)
<b>Hypertension</b>		
• Yes	23(59%)	20(51.3%)
• No	16(41%)	19(48.7%)
<b>Tolerability and side effects</b>		
• 0	34(87.2%)	36(92.3%)
• 1(Somnolence)	3(7.7%)	2(5.1%)
• 3(Constipation)	2(5.1%)	1(2.6%)

Regarding comparing efficacy in both the groups, the mean VAS in group A was  $7.46 \pm 0.99$  before the treatment and  $4.17 \pm 0.72$  after 8 weeks. In group B, the mean VAS before and after the treatment was  $7.35 \pm 0.978$  and  $2.79 \pm 0.832$ .

This reduction was statistically significant both within the groups and in comparison to the two groups. (p-value < 0.001).

**Table 2. Comparison of Pain on Visual analog scale in both groups**

Groups	Mean Value		p-value	Mean Reduction	p-value
	Before Treatment	After Treatment			
<b>Group A</b>	7.46 ± 0.99	4.17 ± 0.72	<0.001	3.29 ± 1.09	<0.001
<b>Group B</b>	7.35 ± 0.98	2.79 ± 0.83	<0.001	4.56 ± 1.33	

## Discussion

Diabetic neuropathy, one of the microvascular complications of diabetes, is responsible for a concerning consequence: diabetic foot ulcers, present in 50% of patients (Boulton, 2014). The treatment for this condition is suboptimal, with a "good" response to standard medication resulting in only a 30-50% pain reduction (Bril et al., 2011). Available medications are often moderately effective, and adverse effects limit their use. Furthermore, recent reviews of new medications for painful diabetic neuropathy have failed to demonstrate efficacy. Therefore, it is crucial to investigate new mechanisms and treatments for this condition (Alam et al., 2021).

Due to the ineffective effectiveness of different drugs, we conducted a study comparing a standard drug (duloxetine) with a standard drug plus vitamin D. Upon a detailed literature review, we found no studies comparing these two groups. There was no significant difference between both groups regarding gender or comorbidities. However, when comparing the Visual Analog Scale (VAS) at 8 weeks, the p-value was 0.001, indicating a significant difference in pain reduction.

A randomized controlled trial conducted by Wu CS et al. showed that duloxetine is more effective than a placebo in people with painful diabetic peripheral neuropathy. There was a significant improvement in pain compared to the placebo group. If a 60-mg dose is inadequate, increasing the dose to 120 mg of duloxetine may alleviate symptoms of painful diabetic peripheral neuropathy. Goldstein et al. discovered that the duloxetine group experienced a more than 50% decrease in pain levels compared to the placebo group. A comprehensive review by Sultan et al. found a similar reduction of >50% in pain scores. Still, they also noted discontinuation of duloxetine due to adverse effects such as nausea (29%), somnolence (14%), and others (Goldstein et al., 2005; Sultan et al., 2008). Similar positive outcomes have been demonstrated in investigations by Smith and Wernicke et al. However, even with dose escalation in these studies, complete pain relief was not achieved, necessitating additional interventions for optimal pain management (Smith, 2006; Wernicke et al., 2006).

While no direct comparison is found in the literature, a systematic review suggests that supplementing with vitamin D may be beneficial in treating painful peripheral diabetic neuropathy. Pain relief may be associated with adequate vitamin D after supplementation (Yamine et al., 2020). Furthermore, a strong link between vitamin D insufficiency and diabetic neuropathy has been established, with vitamin D deficiency identified as a risk factor for developing the condition (Qu et al., 2017). Vitamin D deficiency is common in diabetic patients, and low levels are associated with the presence and severity of sensory neuropathy. Retrospective research suggests that vitamin D insufficiency is an independent risk factor for diabetic peripheral neuropathy (Shehab et al., 2012; Wang et al., 2015).

The exact mechanism behind symptom improvement with vitamin D supplementation remains unclear. It is uncertain whether the improvement is due to an increased pain threshold, improved function of the affected nerves, or both (Shehab et al., 2015). The biological action of vitamin D on the nervous system involves the production of enzymes involved in neurotransmitter synthesis and chemicals

implicated in brain detoxification pathways. Vitamin D also increases the activity of nerve growth factor (NGF), a protein essential for forming and maintaining various populations of neurons in the peripheral nervous system (Carlson and Kenny, 2007).

However, as previously mentioned, there is currently no available data comparing the combination of duloxetine and vitamin D with duloxetine alone in managing diabetic neuropathy. This was the main reason for further exploring this combination in managing diabetic peripheral neuropathy. Further trials are needed to obtain more detailed and comprehensive results on this combination.

## Conclusion

The combination of duloxetine and vitamin D group proved superior to the duloxetine group. And there is a significant decrease in VAS score. As no data regarding this study was available, more studies in this field are needed.

## Declarations

### Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

### Ethics approval and consent to participate.

Approved by the department Concerned.

### Consent for publication

Approved

### Funding

Not applicable

## Conflict of interest

The authors declared an absence of conflict of interest.

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