

## COMPARISON BETWEEN THE EFFICACY OF PREGABALIN AND AMITRIPTYLINE IN ALLEVIATING PAIN ASSOCIATED WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY

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### ABSTRACT

**Objective:** To compare the efficacy of pregabalin and amitriptyline in alleviating pain associated with painful diabetic peripheral neuropathy (PDPN).

**Study Design:** Randomized controlled trial.

**Place and Duration of Study:** Department of Medicine, Pakistan Naval Ship (PNS) Shifa Karachi, from May 2014 to Nov 2014.

**Material and Methods:** Six hundred and sixty patients (330 in each group) with PDPN fulfilling the inclusion/exclusion criteria were randomized into groups A & B through consecutive non-probability sampling. Baseline pain scores on visual analogue scale (VAS) from 0-10 were recorded. Group-A was given pregabalin & group-B was given amitriptyline. Response was assessed after 6 weeks using VAS. A reduction of >50% on VAS was labeled efficacious.

**Results:** Out of 660 patients, 46.36% (n=153) in group-A and 57.88% (n=191) in group-B had effective relief of pain whereas 53.64% (n=177) in group-A and 42.12% (n=139) in group-B had persistent pain. A *p*-value was calculated as 0.003.

**Conclusion:** Amitriptyline was significantly more effective for alleviation of pain associated with PDPN when compared with pregabalin.

**Keywords:** Alleviation of pain, Amitriptyline, Painful diabetic peripheral neuropathy, Pregabalin.

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### INTRODUCTION

Diabetes mellitus (DM) is the 4<sup>th</sup> leading cause of death among non-communicable diseases, accounting for 1.5 million global deaths each year<sup>1</sup>. Diabetes is very common globally showing prevalence of about 9% in 2014<sup>2</sup>. Prevalence in Pakistan is even higher with 16.68% in males and 19.37% in females<sup>3</sup>. Painful diabetic peripheral neuropathy (PDPN) is the most common complication of long standing DM<sup>4</sup> with prevalence ranging from 6% to 34%<sup>5</sup>. Poor glycemic control, especially greater variations in glucose levels, contributes to the occurrence and severity of PDPN<sup>6</sup>. Typical symptoms include burning pain, paresthesias, and numbness in a glove and stocking pattern with proximal progression<sup>7</sup>. Achieving tight

glycemic control is the corner stone in the management of PDPN<sup>8</sup>. Pregabalin and Amitriptyline are usually recommended as first-line treatment for PDPN<sup>9,10</sup>.

We conducted this study as no statistics are available regarding the efficacy of pregabalin and amitriptylin in our local population. Although pregabalin is used more frequently as compared to amitriptyline but later is cost effective. We aimed to explore a suitable treatment regimen for Pakistani population which should be more efficacious.

### PATIENTS AND METHODS

This randomized controlled trial was carried out from Apr 2014 to Oct 2014 at PNS Shifa Karachi, which is a tertiary care centre. Permission from hospital ethical review committee was taken. Sample size was calculated using WHO calculator for sample size determination in health studies keeping confidence

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level at 95%, power of study at 80%, difference in success rate at 61.9% and 51.1% in both groups<sup>10</sup>. A total number of 660 (330 in each group) were selected through consecutive non-probability sampling after taking informed written consent. Patients were divided into two groups by random number generation. Diabetic patients of age from 16-60 years diagnosed to have PDPN were included in the study. Patients who were suffering from chronic medical ailments like CKD, CLD, SLE, RA, epilepsy, psychiatric illness, malignancy and substance abuse (all these conditions can cause neuropathic pains thus acting as confounders), pregnant women or those intending to conceive, lactating mothers, patients taking anticonvulsants, antidepressants, local anaesthetics and opioids were excluded.

Patients were randomly divided into two groups (A & B) by random number generation. It

questionnaire (attached) with demographic profile.

Statistical analysis was done using SPSS version 17. The descriptive statistics like Age and Pain Score on VAS were presented in the form of mean  $\pm$  standard deviation (SD) whereas categorical statistics like gender in frequency and percentages. Student t-test was applied to determine statistical difference in pain score in both groups after every two weeks and median reduction after 6 weeks i.e. end of treatment. Chi square test was used to determine the statistical difference in categories of response to medications i.e. mild, moderate and good on the basis of reduction in pain score on VAS. A *p*-value  $<0.05$  was considered as significant. Results were presented with help of tables.

## RESULTS

A total of 660 subjects (330 in each group)

**Table-I: Age-wise distribution in both the groups.**

Age (years)	Pregabalin Group-A (n=330)		Amitriptyline Group-B (n=330)	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
16-40	76	23.03	81	24.55
41-60	254	76.97	249	75.45
Total	330	100	330	100
Mean $\pm$ SD	47.23 $\pm$ 7.09		46.76 $\pm$ 7.04	

**Table-II: Gender-wise distribution in both the groups.**

Gender	Pregabalin Group-A (n=330)		Amitriptyline Group-B (n=330)	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
Male	193	58.48	178	53.94
Female	137	41.52	152	46.06
Total	330	100	330	100

was a single blind study. Complete history and physical examination to look for various micro & macro vascular complications of DM was done. PDPN was diagnosed by using Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score. Group-A was administered pregabalin starting from 75 mg daily to max 150 mg twice daily and group-B was administered amitriptyline 25 mg at night after stopping previous treatment and washout period of one week. Mean pain score was assessed at baseline and after 6 weeks in all patients according to severity of pain on VAS. Data was collected on a structured

fulfilling the inclusion/exclusion criteria were enrolled. Age distribution of the patients showed that 23.03% (n=76) in group-A and 24.55% (n=81) in group-B were between 16-40 years of age while 76.97% (n=254) in group-A and 75.45% (n=249) in group-B were between 41-60 years of age. Mean  $\pm$  SD was calculated as 47.23  $\pm$  7.09 and 46.76  $\pm$  7.04 years respectively (table-I). Gender distribution of the patients showed that 58.48% (n=193) in group-A and 53.94% (n=178) in group-B were males while 41.52% (n=137) in group-A and 46.06% (n=152) in group-B were females (table-II). Comparison of mean pain score

at baseline was calculated as  $3.43 \pm 0.87$  in group-A and  $3.51 \pm 0.82$  in group-B,  $p$ -value was 0.225. After 6 weeks of treatment it was  $2.18 \pm 0.67$  in group-A and  $1.89 \pm 0.64$  in group-B,  $p$ -value was 0.000 (table-III). Comparison of efficacy of pregabalin and amitriptyline in alleviating pain associated with PDPN showed that 46.36% (n=153) in group-A and 57.88% (n=191) in group-B were treated effectively while 53.64% (n=177) in group-A and 42.12% (n=139) in group-B were not treated effectively,  $p$ -value was calculated as 0.003 (table-IV).

## DISCUSSION

Patients with PDPN have major negative impact on the quality of their life due to daily occurrence of symptoms. Medications of several different classes are used to treat painful DPN with varying degrees of efficacy, safety and tolerability<sup>9</sup>. However total pain control with

significant difference between the treatments. Drowsiness was the commonest side effect in both groups (Pregabalin - 20%, Amitriptyline - 43%)<sup>11</sup>. In another study of 69 patients, 23 out of 45 treated with pregabalin (51.1%) and 13 out of 21 patients (61.9%) treated with amitriptyline were labeled successful with the drugs<sup>12</sup>.

Bansal and colleagues<sup>12</sup> compared the efficacy and safety of pregabalin and amitriptyline in alleviating pain associated with PDPN, they recorded good, moderate and mild pain relief in 21 (48%), 6 (13%) and 7 (15%) patients on pregabalin and 15 (34%), 5 (11%) and 12 (27%) patients on amitriptyline respectively, by patient's global assessment of efficacy and safety. Patient and physician's global assessment, McGill pain questionnaire, Likert pain scale and Patient Global Impression of change showed no significant difference between the treatments,

**Table-III: Comparison of mean pain score at baseline and 6 weeks.**

Pain on VAS	Pregabalin Group-A (n=330)	Amitriptyline Group-B (n=330)	$p$ -value
At baseline	$3.43 \pm 0.87$	$3.51 \pm 0.82$	0.225
At 6 weeks	$2.18 \pm 0.67$	$1.89 \pm 0.64$	0.000

**Table-IV: Comparison of efficacy of pregabalin and amitriptyline in alleviating pain associated with PDPN.**

Efficacy	Pregabalin Group-A (n=330)		Amitriptyline Group-B (n=330)		$p$ -value
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)	
Yes	153	46.36	191	57.88	0.003
No	177	53.64	139	42.12	
Total	330	100	330	100	

monotherapy often remain inadequate and most patients require a combination of agents to achieve satisfactory pain control<sup>11</sup>.

The findings of our study are in agreement with a study of 69 patients with PDPN, 13 out of 21 patients (61.9%) treated with amitriptyline and 23 out of 45 patients treated with pregabalin (51.1%) were shown to get benefit in term of pain relief<sup>12</sup>.

In a randomized control trial for analgesic effects of pregabalin and amitriptyline; good, moderate and mild pain relief were noted in 21 (48%), 6 (13%) and 7 (15%) patients on pregabalin and 15 (34%), 5 (11%) and 12 (27%) patients on amitriptyline, respectively. Results showed no

although improvement with both treatments was seen from the first week. Of the 52 adverse events reported, 34 (65.4%) were with amitriptyline, drowsiness being the commonest (in 19 (43%) patients). Pregabalin caused adverse events in 18 (25%), of which drowsiness was the most common in nine (20%) patients. We could not evaluate these side effects in our study. They concluded that there were few differences between the two treatments in efficacy, pregabalin 150 mg twice daily might be the alternative choice as it was associated with fewer adverse effects in our population.

However, Boyle and others<sup>13</sup> in a randomized placebo controlled trial concluded that

there was no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin in patients with PDPN, which is in contrast with the findings of our study.

This magnitude is primary in our population, other trials are required to validate our findings, however, our results with the support of other studies support amitriptyline in alleviating pain associated with PDPN as compared to pregabalin, which is beneficial as amitriptyline is cost effectiveness when compared to pregabalin.

### CONCLUSION

We concluded that amitriptyline was significantly more effective for alleviation of pain associated with PDPN when compared with pregabalin.

### CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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