

**A COMPARITIVE STUDY ON PREGABALIN VERSUS PREGABALIN  
WITH DULOXETINE IN PATIENTS WITH DIABETIC PERIPHERAL  
NEUROPATHY AND IMPACT OF PATIENT EDUCATION ON QUALITY  
OF LIFE AND MEDICATION ADHERENCE**

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## **ABSTRACT**

**Background:** The study aimed to compare the efficacy and safety of pregabalin versus pregabalin with duloxetine and the impact of patient education on quality of life and medication adherence in these patients.

**Method:** This prospective observational study was conducted for a period of 6 months, among 150 patients aged 18 years and above who had diabetic peripheral neuropathic pain prescribed with pregabalin alone or pregabalin with duloxetine. The patients were divided into 2 groups, group A was prescribed pregabalin alone and group B was given pregabalin with duloxetine. Secondly, the impact of patient education on QoL and medication adherence were assessed in the control and intervention group, in which the latter group was given patient counseling. Statistical analysis of the study was done using independent and paired t test. Analysis of the results was done using self validated questionnaire for pain score, self validated questionnaire for quality of life, and MMAS 8 (Morisky Medication Adherence Scale) for medication adherence.

**Result:** Out of 150 patients, 32 patients (42.6%) taking pregabalin and 51 patients (68%) taking pregabalin with duloxetine had pain relief, indicates better efficacy for pregabalin with duloxetine. The ADR observed with pregabalin was 2.6% and pregabalin with duloxetine was 8%, indicates better safety profile for pregabalin as monotherapy. There was significant improvement in QoL of intervention group (50.67%) compared to control group (32%). The medication adherence improved in both groups respectively.

**Conclusion:** Based on our study it was concluded pregabalin has better tolerability and safety compared to pregabalin with Duloxetine. But the latter is more effective in treating DPN patients. There was a remarkable impact of patient education on QoL, however no significant impact on medication adherence.

**KEYWORDS:** Pregabalin, Duloxetine, Diabetic Peripheral Neuropathy, Quality of Life, MMAS 8, ADR reporting form, Medication adherence.

## **INTRODUCTION**

Diabetes is a significant public health issue that has reached epidemic proportions worldwide(1). A major complication of diabetes is diabetic neuropathy, which affects 50% of individuals with diabetes(2). Diabetic neuropathy is defined as the type of nerve damage that is caused by diabetes(3). Peripheral neuropathy, autonomic neuropathy, focal neuropathy and proximal neuropathy are the types of diabetic neuropathy(4). Among them, Diabetic Peripheral neuropathy (DPN) is the most common( affects 28% and 49%) affecting the legs, feet , hands and arms(2,5).

Gradual onset of prickling, numbness or tingling in feet or hands, sharp throbbing, aching, shooting, stabbing or burning pain are the symptoms of DPN(6). Hyperglycaemia sustained over a long period of time ,high level of triglycerides ,low level of vitamin B12,alcohol,hypertension,cigarette smoking, obesity, genetics are the risk factors of DPN(7–9).

The United states Food and Drug Administration has currently approved 2 drugs for the treatment of DPN, they are duloxetine and pregabalin(10). Pregabalin is an anticonvulsant medication that is used to treat neuropathic pain, fibromyalgia and partial onset seizure when used in conjunction with other anticonvulsants(11). Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) has been useful in treating anxiety and depression other than painful DPN(12).Common adverse events associated with these drugs are headache, insomnia, somnolence, dizziness, weight gain, peripheral edema, diarrhoea etc(13,14)

In diabetic patients it is vital to give awareness on leading a quality life to avoid disease-related comorbidities and complications(15). Additionally, medication adherence is a major factor in treatment success(16). Adherence failure impacts not only the patient but also the health care system(17). Pharmacist plays an integral role in the management of diabetic peripheral neuropathy as a part of multidisciplinary approach, to ensure safe and appropriate use of medication for DPN patients(18).

As per our knowledge there are limited head- to -head comparison studies between Pregabalin versus Pregabalin with Duloxetine for DPN. In this study, the 2 main aims were studied respectively: compare the safety and efficacy of Pregabalin versus Pregabalin with Duloxetine as well as analysing the effect of patient counselling on medication adherence and quality of life (QOL) in DPN patients. Because, a prospective

study to evaluate how much effective is one drug to the other in addition to QOL and medication adherence since DPN is a major complication of diabetes worldwide.

## **MATERIALS & METHODS**

This prospective observational study was conducted at department of Neurology at PK DAS hospital, Vaniyamkulam from January 2022 till June 2022. The study was approved by Institutional Ethics Committee of Nehru College of Pharmacy, Pampady, Thrissur. A total of 180 patients with DPN were screened from neurology department of PK DAS hospital. From those 150 patients were included in the study as per inclusion and exclusion criteria.

Patients were eligible for the study if they were more than 18 years of age, experiencing DPN pain associated with Type 1 or Type 2 Diabetes and willing to provide a written consent form. Patients with active diabetes related foot ulceration or painful wound, severe osteoarthritis, history / current diagnosis of mania, BPD, OCD or post-traumatic stress disorder, pregnant and breast-feeding women and also those with other form of neuropathies were excluded by clinical history examination and nerve conduction testing were excluded. The primary objective of the study is to compare the safety and efficacy of pregabalin versus pregabalin with duloxetine, assessed through suspected adverse drug reaction (ADR) reporting form and self validated questionnaire for pain scale. The secondary objective is to assess quality of life, medication adherence using self validated questionnaire for quality of life and Morisky medication adherence -8 questionnaire (MMAS-8), as well as to provide patient education to improve the same.

### **METHODS**

Various validated questionnaires have been used in this study to evaluate the primary and secondary objectives. The efficacy of pregabalin v/s pregabalin with duloxetine was compared by studying patient response to the drug using self validated questionnaire for pain score.

Self validated questionnaire for pain score consist of certain pain descriptors, that are graded on intensity scale as mild (0), discomforting (2), distressing (3), horrible (4), excruciating (5). The maximum pain score that can be obtained is 33 which indicate severe pain and minimum score is zero that indicating no pain. Self validated questionnaire for pain score is divided into 3 categories, 0-11 represents mild pain (high efficacy of drug), 11-22 indicate moderate pain and 22- 33 indicates severe pain.

The safety profile of these two drugs was evaluated by measuring the occurrence of adverse drug reaction associated with each drug using ADR reporting form.

The baseline data to assess the quality of life and adherence of the patients is collected using self validated questionnaire for quality of life and Morisky medication adherence -8 questionnaire. Patient counselling (with the help of patient information leaflet) was provided to a randomly selected intervention group

The MMAS 8 is an 8 item structure , self-report measure that evaluate medication adherence . The total score is sum of 8 questions , with score 8 were regarded to have a high level of adherence ,7 or 6 reflecting medium adherence and score below 6 were considered to have low adherence.

The self validated questionnaire for quality of life has been adapted to provide a quick indicator of patient's perceived emotional, social and physical health concerns in primary care. It consists 20 questions, divided into six subcategories, energy level (2), pain (5), emotional reaction (2), sleep (5), social isolation (2), physical ability (4) with each question carries one point, the sum of all values adds up to 20 points.

Data collected during first follow up and second follow up using specially designed case report form via conducting personnel interviews.

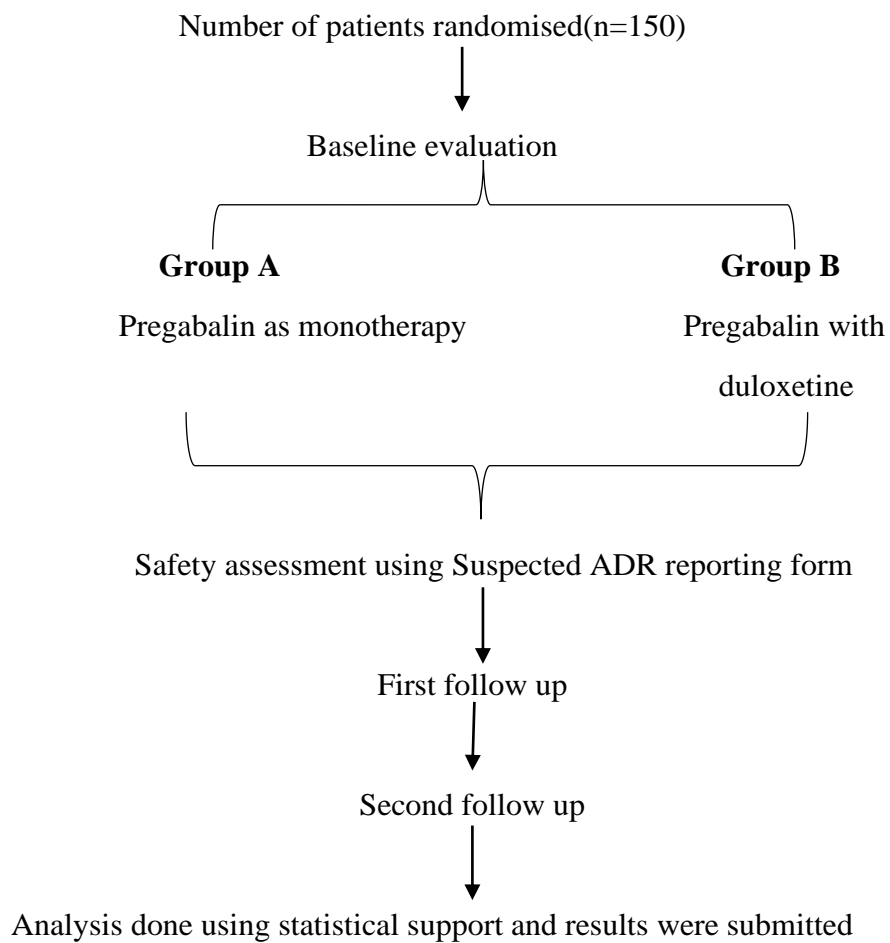


Figure I: shows methodology for safety assessment using ADR reporting form.

## **STATISTICAL ANALYSIS**

The data were entered into Microsoft Excel spreadsheet and further analyzed using statistical software SPSS Version 21.0. The categorical variables were reported as frequency and percentage, whereas continuous variables were presented as mean and standard deviation. Independent and paired sample t tests were used to analyse the quantitative variables. P value of categorical variable were determined using t-test. P value less than 0.05 were considered as statistically significant.

## **RESULTS**

### **Patient demographic details**

The age of study groups was categorized into <50, 50-59,60-69 and >69. In our study population, most subjects were under the age group 60-69 (42%). Among this, patients taking Pregabalin alone under 60-69 category accounted for 36% and Pregabalin with Duloxetine accounted for 48%. Out of 150 patients, 39.33% (59) were males and 60.66% (91) were females. Hence, we could say that females were more affected with diabetic peripheral neuropathy than males. From the total male population (59), 47.45% were treated with Pregabalin as monotherapy and only 52.54% received Pregabalin with Duloxetine. From the total female population (91), 38.46% were treated with Pregabalin and Duloxetine and only 43.95% received pregabalin as monotherapy. The employment status of patients showed that 62% (93) patients were found to be employed and 38% (57) patients were found to be unemployed. Prevalence of type 1 & 2 diabetes among DPN patients - out of 150 Diabetic peripheral neuropathy patients taking pregabalin alone 4.6% (7) were found to be having Type 1 Diabetes Mellitus and 18% (27) with Type 2 Diabetes Mellitus and taking Pregabalin with duloxetine 10.6% (16) with Type 1 diabetes mellitus and 66.6% (100) with type 2 Diabetes Mellitus. Based on the study result, among 150 patients 5.3% of the patients taking Pregabalin as monotherapy and 4 % of patients taking Pregabalin with Duloxetine had DM for a duration of 1-5 years. 14.67 % of patients taking Pregabalin and 24% taking Pregabalin with Duloxetine comes under the range 6-10 years duration. 66.67 % of patients taking Pregabalin and 64% patients taking Pregabalin with duloxetine comes under 11-15 years category. 13.34 % of patients taking Pregabalin and 8% of patients taking Pregabalin with Duloxetine had diabetes for past 16-20 years.

**Comparison on efficacy of pregabalin vs pregabalin with duloxetine**

In this study, out of 150 patients, 75 were treated with Pregabalin and other 75 were given Pregabalin with duloxetine. Using self-validated questionnaire, pain score levels were evaluated and 33.3 % of patients taking Pregabalin were having moderate pain and 66.7% patients were suffering from severe pain during baseline, which slightly improved after first follow up. The data from first follow up as shown in the table depicts that only 14.6 % of patients had mild pain, about 61.3% patients reported moderate pain and 24% patients had severe pain. During second follow up, 46.6 % patient population reported moderate pain and only 10.6% of patients experienced severe pain.

**Distribution of patients based on occurrence of ADR**

The two main adverse effects observed with administration of Pregabalin alone were peripheral oedema (seen in 1.3% of subjects) and drowsiness (1.3%). At the same time more adverse effects were observed when Pregabalin and Duloxetine were administered together such as weight gain (1.3%), somnolence(1.3%), headache(1.3%), drowsiness(2.7%), and fatigue(1.3%).

**QOL and medication adherence assessment**

In this study, out of 150 patients 75 was taken as control (without counselling) and other 75 was taken as intervention (given verbal counselling with patient information leaflet). The score of QoL based on self-validated questionnaire for quality of life were significantly improved in intervention when compared to control group as shown in table II.

**QOL**

In 75 patients of intervention group, 0% had high QOL in the baseline and it gradually increased to 22.67% in the first follow up and then to 50.66% in second follow up. Whereas in case of control group, the percentage of subjects showing high QOL was relatively lower compared to intervention group and was 0% in the baseline that increased to 17.33% in first follow up and to 32% in second follow up. The impact of patient education played a significant role in achieving a huge increase in QOL.



**Table I:** Shows comparison of efficacy of pregabalin and pregabalin with duloxetine using self-validated Questionnaire for pain score.

Sl.no	Efficacy		Number of patients taking pregabalin (n=75)	Percentage (%)	Number of patients taking pregabalin with duloxetine (n=75)	Percentage (%)
I	BASELINE	Mild	0	0%	0	0%
		Moderate	25	33.3%	19	25.3%
		Severe	50	66.7%	56	74.7%
II	FIRST FOLLOW UP	Mild	11	14.6%	18	24%
		Moderate	46	61.4%	51	68%
		Severe	18	24%	6	8%
III	SECOND FOLLOW UP	Mild	32	42.6%	51	68%
		Moderate	35	46.6%	20	26.6%
		Severe	8	10.8%	4	5.4%

**Table II:** Distribution of score among intervention and control group.

QUALITY OF LIFE						
	INTERVENTION GROUP			CONTROL GROUP		
	BASELINE	1 <sup>ST</sup> FOLLOW UP	2 <sup>ND</sup> FOLLOW UP	BASELINE	1 <sup>ST</sup> FOLLOW UP	2 <sup>ND</sup> FOLLOW UP
<b>WORST (0-6)</b>	55.66%	22.66%	12.0%	57.36%	42.67%	20%
<b>MEDIUM (7-12)</b>	41.34%	50.67%	37.34	42.64%	40%	48%
<b>HIGH (13-20)</b>	0%	22.67%	50.66%	0%	17.33%	32%

**Table III:** Distribution of medication adherence among DPN patients.

MEDICATION ADHERENCE				
SL.NO	CATEGORY		CONTROL	INTERVENTION
<b>1</b>	<b>BASELINE</b>	<b>Low adherence</b>	35	37
		<b>Medium adherence</b>	24	23
		<b>High adherence</b>	16	15
<b>2</b>	<b>1<sup>st</sup> FOLLOW UP</b>	<b>Low Adherence</b>	30	23
		<b>Medium Adherence</b>	28	24
		<b>High Adherence</b>	21	28
<b>3</b>	<b>2<sup>nd</sup> FOLLOW UP</b>	<b>Low Adherence</b>	21	11
		<b>Medium Adherence</b>	30	27
		<b>High Adherence</b>	24	37
	<b>TOTAL</b>		75	75

## **DISCUSSION**

In this study, safety and efficacy of pregabalin versus pregabalin with duloxetine were compared in a natural setting. Differences in pain scores from baseline to first follow up and second follow up revealed effectiveness of these drugs. Baseline severity pain scores of 66.6% was reduced to 24% in first follow up and 10.6% in second follow up of patients taking pregabalin as monotherapy. Patients taking pregabalin with Duloxetine showed modest level of analgesic effect in severity pain score of first follow up 8% compared to baseline severity scores 74.6%, which is sharply decreased to 5.3% in second follow up .From these observations, it is found that, at end of study mean pain scores were significantly reduced in both Pregabalin and also in patients taking pregabalin with duloxetine. Therefore, both are found to be effective and well tolerated to reduce pain in DPN patients.

Therefore, results of study favour the use of pregabalin with duloxetine, indicating that this might be a reasonable option for patients with DPN. The observations from this study is equivalent to multinational, randomised research study done by Tesfaye et al.(19)

While assessing safety of pregabalin and pregabalin with duloxetine, the adverse effects were observed in 2.67% of patients taking pregabalin as monotherapy and 8% in patients taking pregabalin with duloxetine. The reports concerning safety of these drugs were in contrast to study done by Tesfaye et al. which showed lack of evidence and required further studies to support safety and efficacy of these drugs(19).

Evaluation of medication adherence using Modified MMAS-8 in DPN patients in both Control and Intervention group, found that compared to baseline both groups shown high adherence towards DPN treatment. In both intervention and control group, low adherent patients were found to have improvement in medication adherence on first and second follow up. By giving patient education with patient information leaflets, helped to improve patient population of low medication adherence and for highly adherent population, in maintenance of medication

adherence. The result is similar to findings presented by Samu et al. which showed significant improvement in medication adherence after patient education(20).

Clinical pharmacist plays a critical role in health care team, to act as a link between physician and patient. Several patients are unaware of their treatment, disease and symptoms. So, when patients are given opportunity to communicate about their concerns regarding lifestyle, medications etc.. Patient approach to disease can be improved to a great extent. In our study, reasons for non-adherence includes feeling of wellbeing, polypharmacy, financial reasons, old age, fear of side effects and lack of family support. Feeling of well being was most reported reason for non-adherence was feeling of well-being in 53(35.34%) patients .

DPN has a significant impact on QOL of patients. From the results obtained, it is found that QOL is often impaired in DPN patients due to pain severity, a finding consistent with observations in a study conducted by S.J. Benbow et al(21). During the study quality of life in both control and intervention groups evaluated using self-validated questionnaire for quality of life

. Patients with worst quality of life in control group was improved in first and second follow up. But, compared to control group, intervention patients were having more improvement in QOL. The results of study show impact of patient education in intervention group.

## **CONCLUSION**

Pregabalin with duloxetine is having more effectiveness and clinical outcome than Pregabalin taken alone. But while considering the safety of these drugs, patients taking pregabalin with duloxetine reported to have more adverse effects than Pregabalin alone. So, we can conclude that Pregabalin with duloxetine is having more effectiveness and a lower safety profile when compared to pregabalin as monotherapy.

While assessing the medication adherence in control and intervention groups, there was significant improvement in both groups compared to baseline scores. Evaluation of Quality of life in DPN patients shown that, intervention group with patient education is having more improvement in QOL than control groups.

### **CONFLICT OF INTEREST**

The authors have no conflict of interest regarding this investigation.

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