Section A-Research paper
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COMPARATIVE EFFICACY AND SAFETY OF PREGABALIN WITH NORTRIPTYLINE AND PREGABALIN WITH DULOXETINE IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHIC PAIN

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Abstract

Neuropathic pain is caused by a primary lesion or dysfunction in the nervous system. It may result from the damage to the central nervous systems (cerebrovascular accident, multiple sclerosis or injury to the spinal cord) or peripheral nervous system (peripheral neuropathy associated with diabetes, post herpetic neuralgia or surgical interventions). Diabetic Peripheral Neuropathic Pain (DPNP) is characterized by a burning, electrical shock type, lancinations and deep aching pains in the lower extremities. It has sudden onset usually affecting the sleep pattern, reducing productivity and quality of life along with mood disturbances. The commonly used medications for the treatment of Diabetic Peripheral Neuropathic Pain are antidepressants, antiepileptics, opioids, analgesics, topical lidocaine and topical capsaicin for symptomatic analgesic therapy. The pharmacological response among individuals with this condition is varied and most treatments are not very effective in more than half of the patients. Treatment options vary from monotherapy to various combination therapies. Many trails were conducted in patients with peripheral diabetic neuropathic pain that proved the efficacy and safety of different treatment options.

Key words: Neuropathic Pain, Nortriptyline, Pregabalin, Duloxetine, Diabetic neuropathy.

INTRODUCTION:

Neuropathic pain, which refers to pain caused by a lesion or disease of the somatosensory system, represents a broad category of pain syndromes encompassing a wide variety of peripheral of central disorders. Neuropathic pain was defined in 1994 by the International Association for the Study of Pain (IASP) as: "pain initiated or caused by a primary lesion or dysfunction in the nervous system". Clinically, neuropathic pain syndromes are characterized by the combination of positive and negative phenomena. The positive phenomena include various painful symptoms, paresthesia and/or dysesthesia, which, by definition, are abnormal non-painful sensations (e.g., tingling, numbness, pins and needles). Negative phenomena usually include neurological sensory deficits in the painful area, together with other deficits (motor, cognitive etc.). Depending on the location of the lesion. Classical etiologies of peripheral neuropathic pain include painful peripheral neuropathies. Post-herpetic neuralgia and traumatic nerve injury. However, many other groups of patients present with mixed pain syndromes involving both neuropathic and non-neuropathic mechanisms, such as lumbar or cervical radiculopathies, which are among the most frequent causes of peripheral neuropathic pain in the general population.

Table 1: Therapy and drugs used in DPNP.

S.No	Therapy	Class
1	1st Line	Gabapentinoids, TCA, SNRI
2	2nd line	Opioids
3	3rd line	Strong opioids, Neurotoxin

Table 2: Dosage Modifications

Pregabalin Immediate release capsule/ solution (Total Daily Dose)	Pregabalin Extended release Tablet (Once Daily Dose)
75 mg	82.5 mg
150 mg	165 mg
225 mg	247.5 mg (3 X 82.5 mg tab)
300 mg	330 mg

AIM and OBJECTIVES:
The study is aimed to evaluate the comparative efficacy of pregabalin and nortriptyline with pregabalin and duloxetine in patients with diabetic peripheral neuropathi pain.

METHODOLOGY:
Study site and Duration: Study is conducted for 5 months between November 2022 to March 2023, comprising of 60 patients who are diagnosed with Peripheral Diabetic Neuropathic Pain, and are taking medications for pain at Neurology department, NRI General and Super Speciality Hospital, Mangalagiri, Guntur Dt, Andhra Pradesh.
Study design: This is a retrospective cohort observational study.

STUDY CRITERIA:
Inclusion criteria:
1. Patients 18 years of age or above
2. Diagnosed with Diabetes mellitus for at least a year.
3. Suffering with neuropathic pain of diabetic origin.
4. Using medications for neuropathic pain (Pregabalin - nortriptyline or pregabalin - duloxetine) for atleast 2 months.
5. Patient who understood the information and provided written informed consent.

Exclusion criteria:
1. Evidence of an end stage disease of a major system (hepatic, renal, respiratory, hematologic, immunologic, cardiovascular, inflammatory, rheumatology).
2. Evidence of sleep pathology that would interfere with the assessment of treatment.
3. Currently receiving treatment for malignancy.
4. Suffer from seizures including epilepsy.
5. Pregnant, lactating or inadequate contraception.

RESULTS AND DISCUSSION:
A total of 60 patients diagnosed with Diabetic Peripheral Neuropathic Pain who met the inclusion criteria during the study period were included in the study. Efficacy is obtained by using pain scale to the patients.

Demographics:
Age wise distribution:

Table 3: Age wise distribution

S.No	Age groups	Percentage	n=60
1.	31-40	10%	6
2.	41-50	23.33%	14
3.	51-60	40%	24
4.	61-70	18.33%	11
5.	71-80	8.33%	5

Table 3 shows the distribution of study sample according to their age, majority of the subjects 24 (40%) were under the age group of 51-60 years, followed by 14(23.33%) 41-50 years. The mean age of study subjects was 54.68+11.44. Which is in accordance with **Caitlin W Hicks *et al.*,** where the incidence of Diabetic Neuropathic Pain was 40% in age of 40-60 years.

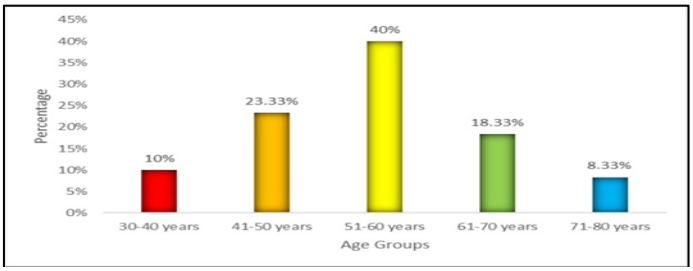

Fig 1: Age wise distribution

Gender distribution:

Table 4: Gender distribution

S.No	Gender	n=60	Percentage
1.	Male	32	53.33
2.	Female	28	46.66

In our study the prevalence of male preponderance 32(53.33%) was higher than females 28(46.66%). The results were in accordance with Gogia, Sonalika et al. where the male to female distribution is 64% to 36%.

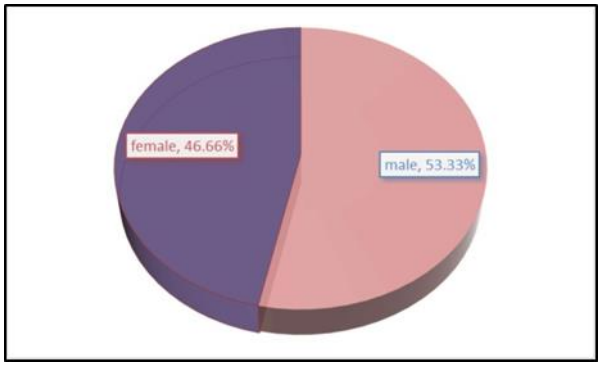

Fig 2: Gender distribution

Duration of Diabetes mellitus:

Table 5: Duration of Diabetes Mellitus

S.No	Duration Of DM	Percentage	n=60
1	1-5 years	28.33%	17
2	6-10 years	43.33%	26
3	11-15 years	11.6%	7
4	16-20 years	15%	9

Table 5 shows the distribution of population based on duration of T2DM, more prevalence is seen in subjects who are having diabetes mellitus for about 6-10 years. About 43.33% of the study population are having T2DM for about 6-10 years with a mean duration of 9.033-5.25. These results are in accordance with Cynthra R *et al*., whose mean duration of diabetes mellitus for the prevalence of Diabetic Peripheral Neuropathic Pain is 8.3 ± 6.7 years.

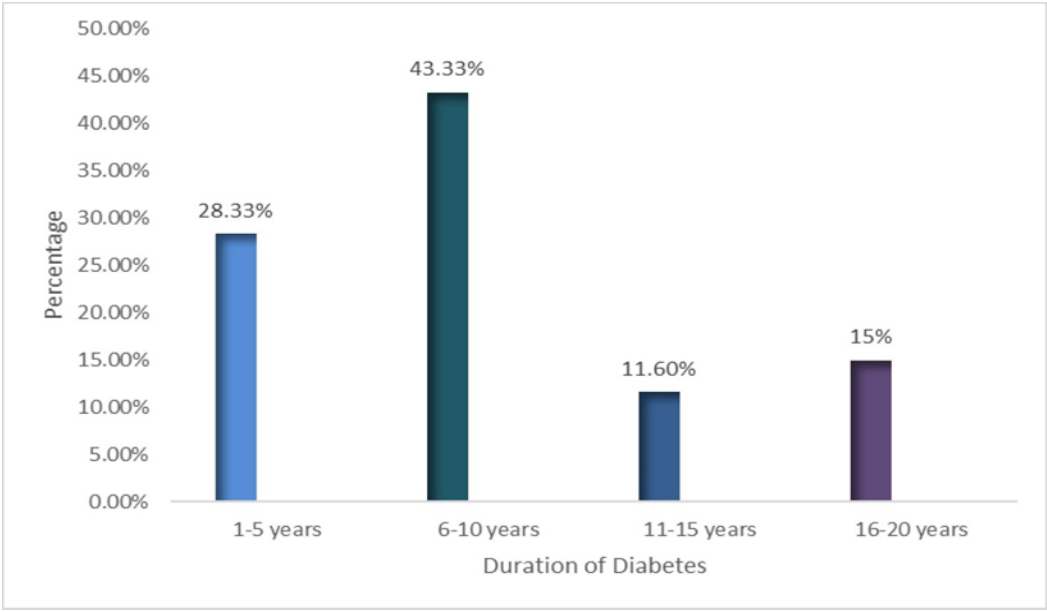

Fig 3: Duration of Diabetes Mellitus

Visual Analouge Scale(VAS) Score:

Table 6: Mean Visual Analouge Score (VAS Score)

Drugs	PG-NT Mean(S.D)	PG-DLX Mean(S.D)
Visit 1	4.233 ± 1.381	4.833 ± 1.839
After 9 weeks	2.758 ± 0.912	2.566 ± 1.304

Table 6 shows mean VAS scores of two groups PG-NT (Pregabalin-Nortriptyline) and PG-DLX (Pregabalin-Duloxetine) at baseline (Visit 1) and at the end of 9 weeks of treatment. A reduction of pain score of 0.9 is considered to be significant reduction of pain in the subjects. In PG-NT group there was a significant difference between the baseline (M=4.233; S.D-1.381) to that of the end of 9 weeks (M-2.758; S.D= 0.912); the mean difference was -1.345 (95% CI -1.654 to -1.035), ($p<0.001$). Similarly, There was a significant difference in PG-DLX group from baseline (M=4.833; S.D=1.839) too.

Mean Insomnia Severity Index Score (ISI)

Table 7: Mean Insomnia Severity Index Score (ISI)

Drugs	PG-NT Mean(S.D)	PG-DLX Mean(S.D)
Visit 1	7.866 ± 3.181	9.7 ± 3.99
After 9 weeks	6.413 ± 2.146	6.833 ± 3.301

Table 7 shows mean ISI scores of two groups PG-NT (Pregabalin-Nortriptyline) and PG-DLX (Pregabalin-Duloxetine) at baseline (Visit 1) and at the end of 9 weeks of treatment. The score ranges from 0-28 where, 0-7 absence of insomnia; 8-14 sub- threshold insomnia; 15-21 moderate insomnia; 22-28 severe insomnia. Betterment in sleep is established with the obtained mean values of both the groups. In PG-NT there is a decrease in the mean ISI score from 7.866 (S.D-3.181) at baseline to a mean score of 6.413(S.D=2.146) at end of 9 weeks mean difference of -1.138 (95% CI -1.612 to - 0.664); ($p<0.001$) on comparison of end of 9 weeks to baseline value. Similarly, the sleep Interference score in PG-DLX is reduced from 9.7(S.D-3.99) at baseline to 6.833(S.D=3.301) at the end of 9 weeks of treatment with a mean difference of -2.867 (95% CI -3.759 to -1.975); ($p<0.001$). Between the two groups the reduction of ISI score is great in PG-DLX when compared to PG-NT. Hence, Pregabalin Duloxetine is more efficacious when compared to Pregabalin-Nortriptyline.

Hospital Anxiety and Depression Scale:

The Hospital Anxiety and Depression Scale (HADS) is used to evaluate the anxiety and depression of the subjects during the course of the treatment. In this, Anxiety and Depression scores are taken separately with the help of a set of questions and the score was given.

0-7 Normal;
8-10 Borderline;
11-21 Abnormal.

Table 8: Hospital Anxiety and Depression Scale – Anxiety score

Drugs	PG-NT Mean(S.D)	PG-DLX Mean(S.D)
Visit 1	8.9 ± 2.77	9.46 ± 4.13
After 9 weeks	7.24 ± 1.52	7.466 ± 2.968

Table 8 shows mean HADS Anxiety scores of two groups PG-NT (Pregabalin- Nortriptyline) and PG-DLX (Pregabalin-Duloxetine). The PG-NT group shows a significant difference in the mean average score of HADS Anxiety score at baseline, 8.9(S.D=2.77) when compared with the mean score at the end of 9 weeks, 7.24(S.D=1.52). The mean difference is -1.414(95% CI -9.17 to -0.90); ($p<0.001$). Similarly, the mean scores at baseline 9.46(S.D-4.13) and at the end of 9 weeks of treatment 7.466 (S.D-2.968) has a mean difference of -2 (95% CI -2.70 to -1.29); ($p<0.001$) shows that PG-DLX group shows more reduction in anxiety scores and is better when compared to Pregabalin-Nortriptyline. This result is in accordance with Solomon Tesfaye, Gordon Sloan *et al*., where Pregabalin-Duloxetine is more efficacious in Anxiety management. Hence Pregabalin-Duloxetine is more significant than Pregabalin-Nortriptyline in management of Anxiety.

Table 9: Hospital Anxiety and Depression Scale – Depression score

Drugs	PG-NT Mean (S.D)	PG-DLX Mean (S.D)
Visit 1	7.266 ± 2.377	7.36 ± 2.42
After 9 weeks	6.34 ± 1.51	5.666 ± 1.825

Table 9 shows mean HADS Depression scores of two groups PG-NT (Pregabalin- Nortriptyline) and PG-DLX (Pregabalin-Duloxetine) seen in visit 1 and at the end of 9 weeks of treatment. The PG-DLX group shows a significant difference in the mean average score of HADS Depression score at baseline, 7.36 (S.D-2.428) when compared with the mean score at the end of 9 weeks, 5.66 (S.D=1.825) where the mean difference is -1.700 (95%CI -2.498 to -0.9024); ($p<0.001$). Whereas there is no significant difference between the baseline and end of 9 weeks of treatment in the PG-NT p=0.076. This result is in accordance with Susan G Ball, Durisala Desaiah et al. (2013). Hence, PG-DLX is more efficacious in managing depression when compared to PG-NT.

Adverse events:
Although not serious some adverse events are reported by the subjects by taking the medications (Pregabalin-Nortriptyline and Pregabalin-Duloxetine). These events were not serious enough to discontinue the treatment. They are shown in Table 10.

Table 10: Adverse events

Adverse drug reactions	DLX- PG n=30 (%)	PG-NT n=30 (%)	Total
Headache	4 (13.33%)	1 (3.33%)	**5**
Abnormal dream & sleep disorder	1 (3.33%)	1 (3.33%)	**2**
Weight gain	1 (3.33%)	2 (6.67%)	**3**
Blurred vision	1 (3.33%)	-	**1**
peripheral edema	1 (3.33%)	-	**1**
uncoodinated body movements	1 (3.33%)	1 (3.33%)	**2**
Total	**9**	**5**	**14**
Percentage	**30%**	**16.67%**	**23.33%**

From Table 10 it is evident that a greater number of adverse events were reported by the subjects taking PG-DLX (30%) treatment when compared to subjects taking PG-NT (16.67%). The most commonly complained event is Headache by Pregabalin- Duloxetine which is almost 13.4%. Sleep disorder, weight gain and peripheral edema were complained by only few patients. In subjects taking Pregabalin-Nortriptyline combination, weight gain is frequently complained (6.67%). The results are in accordance with Padmini Devi, Madhu K *et al*., where the adverse effects obtained are mild and occurred in about 12% of all cases. In case of safety parameters, both the drugs have minor side effects and are safe.

CONCLUSION:
Pregabalin-Duloxetine combination therapy is more efficacious than Pregabalin-Nortriptyline combination in reducing the pain score with an improved sleep interference along with management of Anxiety and depression in patients with Diabetic Peripheral Neuropathic Pain. The most common adverse events seen are Headache and Weight Gain, followed by sleep disorder, blurred vison, peripheral edema and uncordinated body movements.
Hence, we conclude that Pregabalin-Duloxetine is more efficacious than Pregabalin-Nortriptyline in management of pain with manageable adverse events when compared to Pregabalin-Nortriptyline.

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