The Journal of Teachers Association
ISSN 1019-8555 (Print) & ISSN 2408-8854 (Online)
Frequency: Bi-Annual
DOI: https://doi.org/10.62469/taj.v037i02.09

OPEN ACCESS
Website: www.tajrmc.com
Email: editor@tajrmc.com
Volume-37 | Issue-2 | Jul-Dec 2024

Comparison of Efficacy between Duloxetine and Pregabalin in Painful Diabetic Neuropathy

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Abstract: ***Background:*** Painful peripheral neuropathy is a common consequence of long-term diabetes mellitus that impairs quality of life. Pregabalin (an anticonvulsant) and Duloxetine (a new SNRI) are frequently recommended for diabetic peripheral neuropathic pain. ***Methods:*** This randomized clinical trial on painful diabetic neuropathy patients was conducted in the Department of Pharmacology and Therapeutics at Rajshahi Medical College, Rajshahi, in collaboration with the Diabetic Association General Hospital (RADAS), Rajshahi, on 110 patients for one year, from July 2022 to June 2023 after obtaining consent from them. The study population was separated into two groups (Groups A and B) based on drug allocation. For 12 weeks, 55 patients in Group-A received Duloxetine 30 mg twice daily (study group), while 55 patients in Group-B received Pregabalin 75 mg twice daily (control group). The VAS score was assessed at baseline and again at the end of four, eight and twelve weeks of drug treatment. ***Results:*** The mean age of the patients in Duloxetine group was 50.25±7.42 years and Pregabalin group was 49.53±7.84 years. The effect of two drugs on painful diabetic neuropathy was almost equal and the reduction of VAS score between the two groups was statistically non-significant ($p > 0.05$). At the full course of treatment, Duloxetine is cost-effective in comparison to Pregabalin. ***Conclusions:*** In terms of efficacy, Duloxetine or Pregabalin may be used to treat painful diabetic peripheral neuropathy.

Keywords: Efficacy, Duloxetine and Pregabalin.

Original Research Article

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How to cite this article:
Islam MM, Moni SY, Ripon SH, Rahman MH, Rozi SS, Azad M, Jahan N; Comparison of Efficacy between Duloxetine and Pregabalin in Painful Diabetic Neuropathy. Taj 2024;37 (2): 61-68.

Article history:
Received: August 26, 2024
Revised: October 18, 2024
Accepted: November 12, 2024
Published: December 01, 2024

Article at a glance:

Study Purpose: *The purpose of this study was to examine the efficacy of duloxetine with pregabalin in painful peripheral neuropathy.*
Key findings: *The effect of two medications on painful diabetic neuropathy was nearly identical and the reduction in VAS score between the two groups was not statistically significant ($p > 0.05$).*
Newer findings: *Duloxetine is less expensive than pregabalin.*
Abbreviations: *BMI: Body mass index, DPNP: Diabetic peripheral neuropathic pain, RADAS: Diabetic Association General Hospital, T2DM: Type 2 Diabetes Mellitus and VAS: Visual Analogue Scale.*

INTRODUCTION

Diabetes Mellitus (DM) is an endocrine metabolic disorder marked by hyperglycemia and appears to be a significant public health concern due to its earlier onset and growing incidence. Diabetes mellitus has reached in epidemic proportions globally with 700 million people estimated to have the condition by 2045.1 Two-thirds of diabetics live in cities and three out of four are in working age. Patients with long-term diabetes are at risk of acquiring a number of problems and approximately 25% of persons with

Type 2 Diabetes Mellitus (T2DM) have diabetes complications at the time of initial diagnosis.2 Diabetes can cause micro-vascular complications such as retinal, renal and neuropathic disease, as well as macro-vascular issues including coronary artery and peripheral vascular disease.

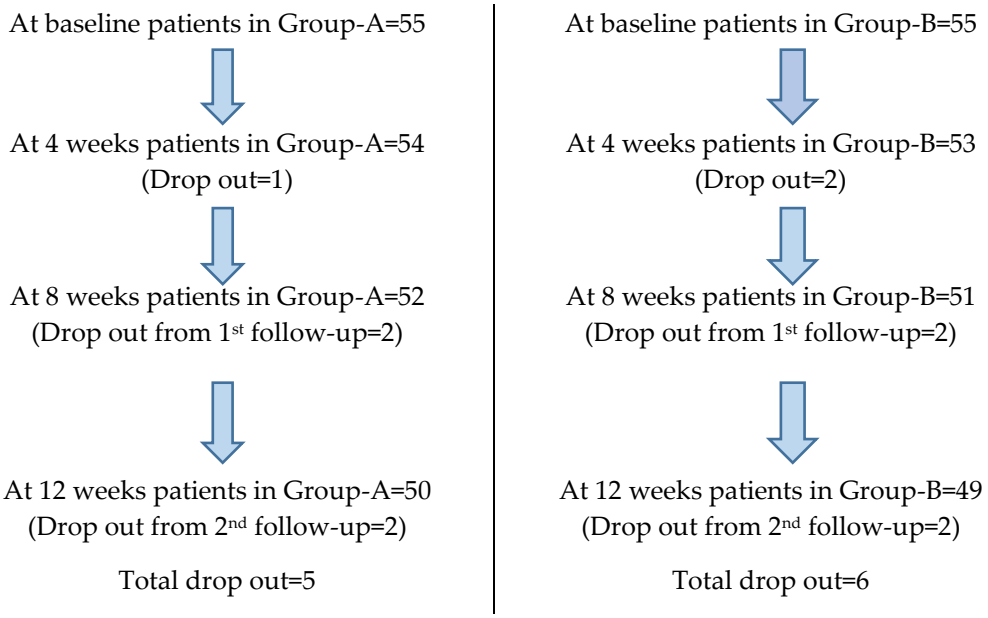
Among the many consequences, diabetic peripheral neuropathic pain (DPNP) is one of the most common causes of neuropathic pain. It affects approximately 10% to 47% of diabetic people worldwide3 and it worsens 25% of Type 2 diabetes cases. Diabetic neuropathy affects both the autonomic and peripheral nerves and has a significant impact on diabetes-related morbidity and reduces quality of life. DPNP causes three separate types of pain: dysphasia, paresthesia and muscle electrical shock-like pain. Patients may also experience allodynia, hyperalgesia and intensely painful coldness. These symptoms start in the lower extremities and proceed to the hands as the disease progresses and they are known as the stock and glove model. The patient's activity reduces over the day due to a sense of walking on sand and rock.4 PDPN not only causes pain but also interferes with patients' sleep, as it worsens during the night, as well as their emotions, mental state and daily activities, resulting in a terrible quality of life and a major financial burden. Because of the multiplicity of pathophysiological processes leading to pain, doctors may find it challenging to diagnose, treat and manage PDN.5,6

It is commonly acknowledged that hyperglycemia's harmful effects contribute significantly to the development of DPNP. Diabetic neuropathic pain is treated primarily by excluding other causes of painful peripheral neuropathy, enhancing glycemic control as a preventative measure and using pain relief drugs. Anticonvulsants such as Pregabalin and Gabapentin, as well as antidepressants, are first-line treatments for pain alleviation. They work by blocking the reuptake of serotonin and noradrenaline. Furthermore, there is experimental and clinical evidence that opioids can be effective in pain management, particularly when used with first-line medications. Other medications, such as capsaicin cream and lidocaine patches have been recommended as adjuvants in the treatment of diabetic neuropathic pain but there is little clinical evidence to justify their use. Currently, three drugs are routinely used to treat DNP: duloxetine, a selective serotonin and norepinephrine reuptake inhibitor; pregabalin, an anticonvulsant and tapentadol, a dual-effect opioid receptor agonist and norepinephrine reuptake inhibitor. However, because pain treatment is ineffective for the majority of patients, numerous pharmacological approaches have been implemented based on pre-clinical and/or clinical evidence, as well as an inference of mechanism of action. Some recent trials compared the efficacy of Duloxetine and Pregabalin around the world, however there have been few investigations on the topic in Bangladesh. Because there has been no recent study comparing the efficacy and safety of Duloxetine to Pregabalin in Bangladesh, the purpose of this study was to assess the efficacy and safety of Duloxetine and Pregabalin for pain management in diabetic neuropathy.

METHODS

A total of 110 painful diabetic neuropathy patients with Type 2 diabetes mellitus who met the eligibility criteria were recruited in the study. All consenting patients within the age group of 30-70 years who were diagnosed by the endocrinologist clinically were included in the study. After informed written consent, the patient’s personal and disease history were obtained and recorded in the data-sheet. The patients were examined by the designated physicians and they were evaluated on the basis of VAS score. Patients were randomly allocated into groups A and B for allotment of the respective drugs. Out of the 110 patients, 55 received tablet Duloxetine 30 mg twice daily (study group) for 12 weeks and the other 55 received tablet Pregabalin 75 mg twice daily (control group) for 12 weeks orally. Patient compliance was assessed by the pill-count method on every visit. Patients were instructed to consult the physician immediately if any unusual side effects occur before the follow-up date. They were followed up at four-weeks intervals until the completion of treatment and during each visit, the VAS score was evaluated and recorded for statistical analysis. The therapeutic efficacy was evaluated after completion of treatment on the basis of reduction of diabetic neuropathic pain. In the study the Batch No of Pregaben and Duloxen was 22001 to 22007. SPSS software, version-24 was used to analyze the data

and the efficacy was compared between the two groups by repeated measure ANOVA statistics. All tests were judged statistically significant with a p-value of < 0.05.



Flow chart: Allocation of patients in the study

RESULTS

The mean ages of the patients in the Duloxetine and Pregabalin groups were 50.25±7.42 and 49.53±7.84 years, respectively with mean duration of diabetes mellitus was 6.15±4.57 years in Duloxetine group and 6.34±4.37 years in Pregabalin group. Gender distribution of the patients revealed that in Duloxetine group, majority (63.60%) of the patients were female but in Pregabalin group, 52.70% were male. There was no significant difference between the two groups in terms of BMI and occupational status (p=0.82 and p=0.23, respectively) (Table 1).

Table 1: Comparison of baseline variables between the two groups (n=55 in each group)

Variables		Group		p-value
		Duloxetine group (n=55)	Pregabalin group (n=55)	
Mean age (Years)		50.25±7.42	49.53±7.84	0.62#
Mean duration of disease (Years)		6.15±4.57	6.34±4.37	0.83*
	Gender			
	Male	20 (36.40%)	29 (52.70%)	0.12*
	Female	35 (63.60%)	26 (47.30%)	
BMI (Kg/m²)				
	Underweight (< 18.5)	5 (9.10)	3 (5.50)	0.82*
	Normal (18.5 to 24.9)	28 (50.90)	30 (54.50)	
	Overweight (25 to 29.9)	12 (21.80)	14 (25.50)	
	Obese (30 to 39.9)	10 (18.20)	8 (14.50)	
Occupational status				
	Housewife	11 (20.00)	6 (10.90)	
	Day labour	6 (10.90)	11 (20.00)	
	Service holder	16 (29.10)	19 (34.50)	0.23*
	Businessman	18 (32.70)	15 (27.30)	
	Others	4 (7.30)	4 (7.30)	

Evaluation of VAS score at four different times revealed that the reduction of VAS score between the two groups was statistically non-significant (p > 0.05) (Figure 1).

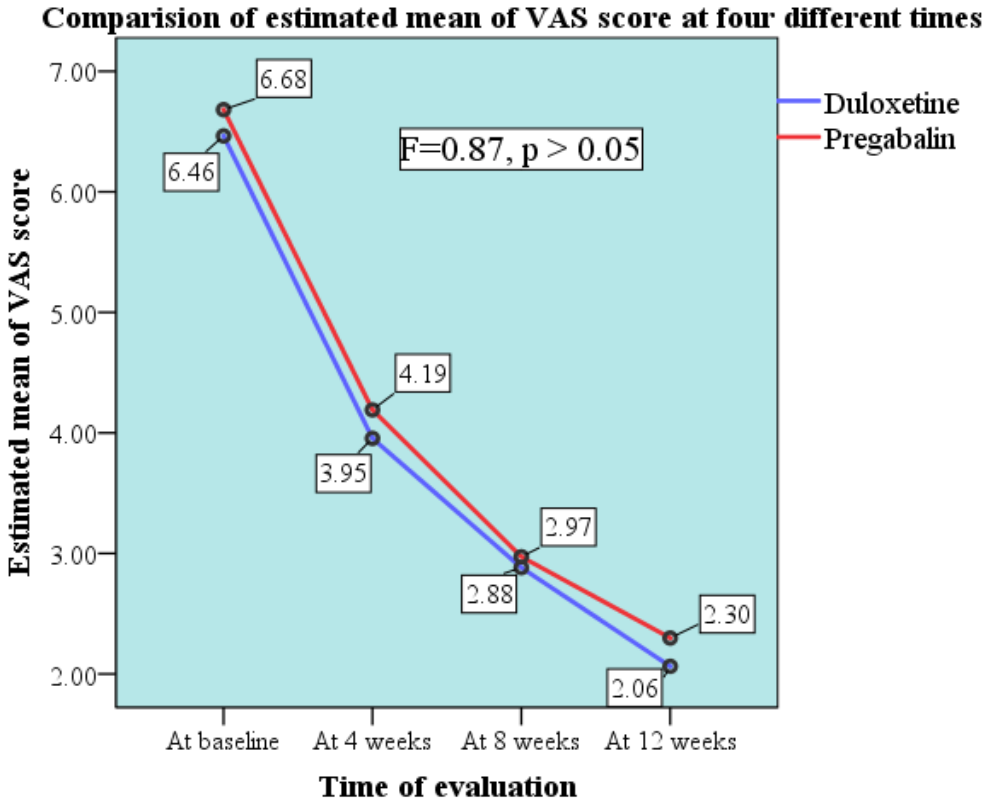


Figure 1: Monitoring of VAS score at different time interval (5 patients in Duloxetine group and 6 patients in Pregabalin group dropped out).

(Data were analyzed with Repeated Measure ANOVA statistics and were presented as mean ± SD.) At the full course of treatment, Duloxetine is cost-effective in comparison to Pregabalin (Table 2).

Table 2: Comparison of cost-effectiveness between Duloxetine and Pregabalin group after 12 weeks (Duloxetine group=50, Pregabalin group=49)

	Duloxetine group	Pregabalin group
Variable	**mean (taka)**	
Cost	1680.00	3024.00

DISCUSSION

Both Pregabalin and Duloxetine are used to treat painful diabetic peripheral neuropathy. Duloxetine is a serotonin and norepinephrine reuptake inhibitor. Its mechanism of action involves the stimulation of serotonergic and noradrenergic activity in the central nervous system's descending inhibitory pain pathways. Pregabalin is within the category of anticonvulsants and inhibits the release of excitatory neurotransmitters implicated in pain perception by binding to presynaptic neuronal calcium channels.

In this study, mean age of the patients in the Duloxetine group was 50.25±7.42 years and Pregabalin group was 49.53±7.84 years. Nearly similar findings were found in a study done by Ahmad et al.[7] where mean age was 51.32±8.90 years and 52.21±8.08 years in Duloxetine and Pregabalin group, respectively. Nearly similar findings were also found with the study done by Shah et al.[8]. Findings were not similar in a study done by Joharchi et al.[9] where mean ages were 54.93±3.70 years and 54.03±4.46 years in Duloxetine and Pregabalin group, respectively. Dissimilar findings were also found with the studies done by Enomoto

et al.[10] and Shabbir et al.[11]. Age influences the presence of diabetic peripheral neuropathy, regardless of other risk factors. Many disorders that cause neuropathic pain increase in occurrence with age, therefore older persons are more likely to experience it than younger adults.

In this study, mean duration of diabetes mellitus was 6.15±4.57 years in Duloxetine group and 6.34±4.37 years in Pregabalin group. Similar findings were found in a study done by Joharchi et al.[9] where mean duration was 9.57±3.20 years and 9.05±2.85 years in Duloxetine and Pregabalin group, respectively. Similar findings were also found with the studies done by Ahmad et al.[7], Shah et al.[8], Enomoto et al.[10] and Shabbir et al.[11]. Dissimilar findings were found in a study done by Shahid et al.[12] where the Duloxetine group had a longer mean duration of diabetes than the Pregabalin group (10.3 ± 1.4 vs. 7.5 ± 1.9 years, respectively).[12] Diabetics with duration of more than three years since diagnosis of diabetes were 7.8 times more likely to develop neuropathy. In the present study, gender distribution of the patients revealed that in the Duloxetine group, majority (63.60%) of the patients were female and remaining 36.40% were male. Similarly, in the Pregabalin group, 52.70% of the patients were male and 47.30% were female. Nearly similar findings were found in a study done by Joharchi et al.[9] where in Duloxetine group, 59.09% were female and 40.91% were male, in Pregabalin group, 62.82% were female and 37.18% were male. Ahmad et al.[7] reported that in Duloxetine group 16 (51.6%) were female and 15 (48.4%) were male and in Pregabalin group 22 (66.7%) were female and 11 (33.3%) were male which were nearly similar with the study. Contradictory findings were found in a study done by Enomoto et al.[10] where in both groups males were predominant. Shabbir et al.[11] found that females were predominant in both groups which findings were not similar with the study.

Though nerve injury and polyneuropathy are more common in males. Females with diabetes report a higher frequency and intensity of pain despite milder neuropathy. Males developed neuropathic complications at 63 years, approximately 4 years earlier than did females (at 67 years).[7] In the present study, in Duloxetine group, the mean VAS score at baseline was 6.46, which decreased to 3.95 at the end of 4 weeks and then to 2.88 at the end of 8 weeks and 2.06 at the end of 12 weeks of drug administration. On the other hand, in the Pregabalin group, the mean VAS score at baseline was 6.68, which decreased to 4.19 at the end of 4 weeks and then to 2.97 at the end of 8 weeks and 2.29 at the end of 12 weeks of drug administration and the reduction of VAS score between the two groups was statistically non-significant ($p > 0.05$). Similar findings were found in a study done by Joharchi et al.[9] where VAS score was 67.23±19.29 in Duloxetine group and 61.74±16.34 in Pregabalin group after treatment. Similar findings were also found with the studies done by Boyle et al.[13], Tanenberg et al.[14], Devi et al.[15], Quilici et al.[16], Yasuda et al.[17], Richter et al.[18], Ahmad et al.[7], Raskin et al.[19], Baron et al.[20], Tölle et al.[21], Jiang et al.[22], Enomoto et al.[10] and Parsons et al.[23]. Contradictory findings were found in a study by Shahid et al.[12] where in the Duloxetine group, the mean VAS score decreased from 6.81 ± 0.91 to 4.01 ± 1.12 with 12 weeks of therapy ($p < 0.001$) and in the Pregabalin group, the mean VAS score decreased from 6.99 ± 1.12 to 4.91 ± 0.82 with 12 weeks of therapy ($p < 0.001$). Contradictory findings were also found with the studies done by Tanenberg et al.[24], Goldstein et al.[25] and Shabbir et al.[11]. Dissimilarity might be due to other factors such as social or natural environments, mental condition, nutrition, hypoalbuminemia and dose-response.

CONCLUSIONS

The study concluded that Pregabalin and Duloxetine were equally effective in treatment of DPNP while none of the drug appeared superior at the 12-weeks of treatment in patients with DPNP but Duloxetine treatment is cost-effective. So, among Duloxetine and Pregabalin, either drug might be used in treatment of diabetic neuropathy.

Acknowledgements

Contribution of the patients who participated in the study were acknowledged for their co-operation in data collection.

Authors' contributions

MMI, SYM, and SHR: Concept and design, data acquisition, interpretation, drafting and final approval. MMI, MHR, SSR, MA and NJ: Data acquisition, interpretation, drafting, final approval

and agree to be accountable for all aspects of the work.

Declarations

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Conflict of interest

Authors declared no conflict of interest.

Ethical approval

Ethical approval of the study was obtained from the Ethical Review Committee, Rajshahi Medical College, Rajshahi. Informed consent was taken from all participants. All the study methodology was carried out following the relevant ethical guidelines and regulations.

Consent for publication: Taken

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The Journal of Teachers Association
Abbreviated Key Title: TAJ
Official Journal of Teachers Association Rajshahi Medical College