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Original Research Article

An Observational Study on Effectiveness and Safety of Amitriptyline, Duloxetine, and Pregabalin in Painful Diabetic Neuropathy

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Abstract:

Background: Peripheral neuropathic pain (DPNP) in diabetics is prevalent and frequently bothersome. The majority of guidelines suggest starting DPNP patients with amitriptyline, duloxetine, pregabalin, or gabapentin as an analgesic medication; however, there isn't much comparison data to suggest which is preferable or whether to mix them. The study's objective was to evaluate the safety and effectiveness of Amitriptyline, Duloxetine, and Pregabalin in lowering neuropathic pain and enhancing sleep quality in DPN patients.

Methods: In a prospective and observational trial, 75 outpatients (25 per patient) prescribed any of the aforementioned medications were progressively enrolled. By comparing the mean monthly visual analogue scale (VAS) score from baseline obtained from the pain diary drug effectiveness was evaluated. The Nottingham Health Profile (NHP) questionnaire's overall and domain-wise scores were compared in order to determine QoL. By comparing the frequency of adverse drug reactions (ADRs), safety was evaluated. The Chi-square test and one-way analysis of variance were used to compare the qualitative and quantitative outcome measures, respectively. It was deemed statistically significant when $P < 0.05$.

Results: Between the three medications, there was a comparable difference in mean monthly VAS scores at the end of 4, 8, and 12 weeks. Compared to patients on other medications, PGN patients experienced smaller overall favorable effects as well as in the affective, energy, and sleep domains of NHP. All medications caused drowsiness and vertigo, however PGN caused the least amount of sedation overall.

Conclusion: These three medications all demonstrated comparable effectiveness in lowering diabetic polyneuropathy pain and enhancing the caliber of sleep. In this rural financially deprived group, amitriptyline may be preferred above the other two due to its relative affordability.

Keywords: Diabetes Mellitus, Neuropathic Pain, Pregabalin, Amitriptyline, Randomization, Duloxetine.

Introduction

Over the course of their lifetime, 50% of patients with diabetes develop diabetic peripheral neuropathy, and around half of them experience neuropathic pain. [1] Burning, electric-shock-type, lancinating, and deep-aching pains in the feet, legs, and eventually the upper limbs are signs of diabetic peripheral neuropathic pain (DPNP). [1]

Insomnia, low quality of life, mood disorders, and five times higher health care costs compared to diabetes alone are among the symptoms of moderate-to-severe persistent pain, which affects over 70% of individuals with DPNP. [1,3] The risk of diabetic peripheral neuropathy has been demonstrated to be elevated by chronic hyperglycemia and cardiovascular risk factors. However, the exact risk factors and mechanism of diabetic peripheral neuropathy remain unclear. [1]When it comes to first-line medications for symptomatic analgesic therapy in patients with DPNP, the majority of international guidelines suggest amitriptyline, duloxetine, pregabalin, or gabapentin. Based on Cochrane reviews and meta-analyses, there is strong evidence supporting the effectiveness of each medication; nonetheless, the greatest result for any monotherapy is 50% pain alleviation in less than half of patients, which is frequently accompanied by dose-limiting side effects. [4]

The lack of strong, head-to-head data about which first-line medication to use first and which alternative medication to add in combination when pain relief on monotherapy is not up to par hinders the management of DPNP. [5] The COMBO-DN research demonstrated that the highest dose

monotherapy of both drugs was not more effective than the normal dose combination treatment of pregabalin and duloxetine. [6] Furthermore, it was discovered that combinations of gabapentinoid and tricyclic antidepressants were more effective than monotherapy. [7,8]

These trials, however, had brief treatment durations and were limited in size. [7,8]

Because of the lack of sufficient data, the majority of current guidelines do not advocate combination treatment.4,5 even though doctors utilize them extensively. Patient suffering and medical expenses rise when evidence-based therapy routes are lacking. [3]

Consequently, there is strong justification in this setting for looking for solid data from carefully thought-out, head-to-head comparative trials of treatment pathways (first-line medications and their combinations).

Materials and Methods

From January 2023 to December 2023, this observational study was conducted in the outpatient department (OPD) of the medicine department at the Bhagwan Mahavir Institute of Medical Sciences, Pawapuri, Nalanda, Bihar. We systematically collected 75 outpatients with excruciating DPN who eighteen years were at least old, with a reported HbA1c of less than 8.5% during the preceding three months, and who had been prescribed AMY, DUL, or PGN by their attending neurologist. Patients who during examination had sources of pain other than DPN were not included in the study. After 25 patients had been added to each of the three therapy observation groups, patient recruitment ceased. Prior to their enrollment in the trial, every patient provided written informed consent.

A visual analog scale (VAS) was used to record the degree of pain, with measurements made to the closest millimeter. In order to document their daily pain intensity, study participants were given a monthly pain diary with VAS. This diary was collected and replaced at monthly follow-up visits. For three months, the mean monthly VAS score was determined at the conclusion of each month. The primary end point was determined to be the mean monthly VAS score change from baseline to three months post-treatment.The Nottingham Health Profile (NHP) questionnaire's overall and domain-wise scores were compared in order to determine QOL. [9] The NHP is a self-reported, well-validated tool that evaluates six categories of health-related quality of life (QOL): energy, sleep, pain, physical mobility, emotional responses, and social isolation. [10] It takes a few minutes to complete the questionnaire, which asks you to answer 38 straightforward statements with a yes or no. A score of 100 denotes the presence of every mentioned limitation. Scores range from 0 to 100. By subtracting the total of the relative weights from 100%, one can interpret the results by determining the relative level affected, where 0 denotes poor health and 1 indicates good health. The trial participants were instructed to report any new adverse events during treatment, as well as any known adverse drug reactions (ADRs) related to the prescription medication. For three months, they were checked on on a monthly basis.

All patients' quantitative baseline characteristics were computed collectively and subsequently for each of the three treatment groups individually. The results were reported as mean ± SD or median (25th and 75th percentile) for variables with normal and non-normal distributions, respectively. There were two ways to express qualitative variables: counts (n) and frequencies (%).

Using the student independent t-test, Mann-Whitney U test, or Chi-square test for qualitative variables, the baseline characteristics of the three groups were compared. Using a post hoc pairwise comparison or repeated measures analysis of variance (ANOVA), the within group change in the outcome measures was analyzed. Using a one-way ANOVA test, the three groups' outcome measures were compared. R was used to analyze the data, and it is free software. It was deemed statistically significant when $P < 0.05$.

Results

With the exception of body mass index (BMI), which is displayed in Table 1, the patients in the three therapy groups had identical baseline characteristics. Compared to the other two groups, patients prescribed AMY had a higher baseline BMI.

Table 1: Baseline demographic and clinical characteristics of study participants

Baseline characteristics	Baseline values Mean±SD or median (Q1, Q3) or n (%)			
	Amitriptyline(n=25)	Duloxetine(n=25)	Pregabalin(n=25)	Total(n=75)
Gender				
Female(n)	14	12	14	40
Male(n)	11	13	11	35
Age(years)	58±7	61±9	64±12	61±9
Duration of diabetes(years)	7 (4,10)	10 (6,15)	6(3,11)	7(4,11)
BMI (kg/m^2)	28.7±3.3*	25.9±2.4	26.1±1.7	26.9±2.8
Hypertension(n[%])	14 (56)	12 (48)	11(44)	37 (49)

Dyslipidemia(n[%])	14 (56)	11(44)	14 (56)	39 (52)
HbA_{1c}(%)	7.7±0.5	7.9±0.4	7.8±0.4	7.8±0.5
Mediandose(mg)	25 (10, 25)	30 (20, 30)	75(75,112.5)	

*p<0.05.

Table 2 displays the mean VAS scores at baseline, 4, 8, and 12 weeks. In comparison to the other two groups, the patients in the AMY group had a higher baseline VAS score (P = 0.04). As indicated in Table 2, all three medications resulted in a decrease in the monthly mean VAS scores over time at 4, 8, and 12 weeks relative to their respective baseline values. Table 2 indicates that there was no variation in the VAS scores at 4, 8, and 12 weeks between the groups.

Table 2: Time series mean VAS scores over 3 months

Drug	Baseline	4 weeks	8 weeks	12 weeks
Amitriptyline (*n*=25)	8.6	7.4	6.9	6.2
Duloxetine (*n*=25)	7.6	6.5	6.4	5.8
Pregabalin (*n*=25)	8.0	6.5	5.8	5.3
p-value	0.04	0.06	0.08	0.21

Table 3 presents a comparison of the three groups' mean differences in VAS scores at 4, 8, and 12 weeks from baseline. A one-way ANOVA of the mean difference in VAS scores revealed no variation in the three medications' ability to lessen pain intensity over a three-month period.

Table 3: Mean VAS score difference between baseline and at end of 4, 8, and 12 weeks

Drug	Baseline VAS score(cm)	VAS score difference (cm)		
		4weeks	8weeks	12weeks
Amitriptyline (*n*=25)	8.6±1.3	1.1±0.9	1.7±0.9	2.3±1.1
Duloxetine (*n*=25)	7.6±1.4	1.2±1.1	1.3±1.5	1.9±1.3
Pregabalin (*n*=25)	8.0±1.2	1.5±1.3	2.2±1.4	2.7±1.9
p-value	0.04	0.47	0.06	0.16

P-value compared between the three groups. VAS: Visual analog scale

The initial BMI of the three groups differed statistically significantly, therefore baseline VAS ratings were adjusted using BMI as a covariate using the analysis of covariance (ANCOVA) test. After adjusting for baseline BMI values, the averages of the VAS score differences across the three groups were compared [Table 4]. Even after accounting for baseline variability in BMI, there was no discernible difference in the three medications' efficaciousness.

Comparing the mean monthly VAS scores after adjusting for baseline variability in VAS score was also done using an ANCOVA test. Even after accounting for baseline variability in VAS values, there was no discernible difference in the three medications' efficacy (data not shown).

Table 4: Mean difference of VAS scores after adjusting for baseline BMI variability

Drug	Actual Mean	Estimated Mean	Pairwise comparison based on estimated marginal mean		
			Drugs	Mean difference	Significant[b]
Amitriptyline (*n*=25)	2.32	2.42[a]	DUL PGN	0.58 -0.22	0.60 1.00
Duloxetine (*n*=25)	1.88	1.83[a]	AMY PGN	-0.58 -0.81	0.60 0.17
Pregabalin (*n*=25)	2368	264[a]	AMY DUL	0.22 0.81	1.00 0.17

By comparing the overall and domain-wise ratings on the NHP questionnaire at baseline and after 12 weeks, as indicated in Table 5, the impact of the three medications on the patients' quality of life was evaluated. After 12 weeks, a one-way ANOVA revealed a statistically significant difference in the three groups' combined score as well as the component scores for the energy, sleep, and emotional domains of NHP. Table 5 indicates that patients on PGN had considerably less favorable effects in these NHP areas than patients on AMY or DUL, according to post hoc analysis.

Table 5: Total and domain-wise NHP scores at baseline and at 12 weeks

Variables	AMY(*n*=25)		DUL(*n*=25)		PGN(*n*=25)		*P*-value
	Baseline	12weeks	Baseline	12weeks	Baseline	12weeks	
Energy	0.46±0.28	0.58±0.26	0.39±0.37	0.59±0.32	0.51±0.28	0.50±0.29	0.002**
Pain	0.35±0.20	0.55±0.17	0.35±0.18	0.56±0.19	0.37±0.25	0.59±0.24	0.93
Emotional	0.61±0.30	0.81±0.21	0.51±0.31	0.71±0.28	0.72±0.19	0.75±0.19	0.001**
Sleep	0.29±0.27	0.73±0.25	0.29±0.33	0.73±0.24	0.39±0.28	0.59±0.29	0.001**
Social	0.76±0.25	0.84±0.21	0.74±0.23	0.77±0.25	0.83±0.17	0.86±0.15	0.06
Physical	0.64±0.15	0.70±0.11	0.63±0.21	0.74±0.16	0.61±0.17	0.66±0.18	0.16
Total	3.10±1.21	4.21±0.96	2.92±1.44	4.09±1.28	3.45±1.08	3.95±1.18	0.001**

***P*<0.05 between the groups at 12 weeks by one-way ANOVA: Analysis of variance, NHP: Nottingham health profile

75 patients had a total of 53 documented adverse medication responses. All of them were minor, self-limiting, and didn't call for stopping treatment. Table 6 displays the calculated incidence of adverse effects in each of the three treatment arms over the course of the trial.

The most frequent side effects, which were observed in all three groups, were sedation and vertigo. To determine whether there is a significant difference in the negative impacts among the three groups, Fisher's exact test was used.

Comparing PGN treated individuals to the other two groups, it was discovered that sedation was lowest in these patients (P = 0.001). Some side effects were unusual since they only happened in one treatment group.

Patients treated with AMY alone experienced dry mouth and urine retention, although edema only occurred in the PGN group.

Table 6: Incidence of adverse drug reactions among the three groups

ADRs	AMY(n=25)	DUL(n=25)	PGN(n=25)	Total(n=75)
Sedation(n[%])	11(44%)	10 (40%)	1 (4%)*	22 (29%)
Dizziness(n[%])	3 (12%)	4 (16%)	9 (36%)	16 (21%)
Edema(n [%])	----	----	9 (36%)	9 (12%)
Urinaryretention(n[%])	2 (8%)	----	----	2 (2.6%)
Drymouth(n[%])	4 (16%)	----	----	4 (5.3%)
Total(n[%])	20 (80%)	14 (56%)	19 (76%)	53(70.6%)

**P*<0.05 between the groups by Fischer's exact test. ADRs: Adverse drug reactions

Discussion

The results of this study demonstrated that, over a three-month period, AMY, DUL, and PGN prescribed by the treating physicians were similarly safe and effective for treating DPN patients' pain symptoms. After controlling for baseline variations, the three medications reduced patients' subjective pain perception in a manner consistent with each other, as seen by a comparable improvement in VAS score. The extent and areas in which QOL was improved by the medications varied, nevertheless. While QOL was improved by AMY and DUL, PGN did not demonstrate a comparable advantage. However, compared to AMY or DUL, PGN was linked to a significantly lower incidence of sedation, even though the medications were well tolerated.

Comparing the three medications' actual efficacy in lowering DPN patients' pain levels was the main goal of this investigation. Over a three-month period, the three medications reduced pain intensity to a comparable degree. With AMY, there was a pain decrease of 2.32 ± 1.07, or less than 23%, as measured by the VAS score. This is significantly less than the 40–50% pain reduction with AMY that was observed in earlier studies. [11–13] But compared to the 50–75 mg/day utilized in the other research, the median dose of AMY used in our investigation was 25 (10, 25) mg/day. In our trial, DUL reduced pain by 1.88 ± 1.30, or less than 19%. Prior research comparing DUL against placebo or PGN revealed a 23%–50% decrease in the intensity of pain. [14–16]

Compared to our median dose of 30 (20, 30) mg/day, the DUL dose employed in these investigations was greater at 60 mg/day. This could explain why our study's DUL efficacy was lower than that of the other research. In our study, the pain decrease with PGN was 2.68 ± 1.89, or approximately 26%. Prior research comparing PGN with active medication or a placebo revealed a 43%–60% decrease in pain intensity. [16–20] PGN was

utilized in our investigation at a median dose of 75 (75, 112.5) mg/day, which was significantly less than the 150–300 mg/day used in earlier studies.Since our study was observational, the treating physician determined the appropriate dosage for each patient. Consequently, the dosages of all three medications were those that physicians in our community typically prescribed. Furthermore, our treating physicians believed that the Indian population requires a lower acceptable dose of these medications than does the western population. Similarly, after three to six months longer than the follow-up period of our study treating physicians escalate dosage for individual patients.Over the course of a 28-day treatment period, Boyle et al. randomized and controlled trial comparing these three medications in DPN revealed no discernible differences in terms of efficacy, quality of life, or safety metrics. [21] While the three medications appeared to be equally beneficial in our study, there were notable differences in QoL indicators that were not present in the earlier investigation. PGN was shown to be less effective than AMY or DUL in our study in raising overall NHP scores. Upon doing separate analyses of each domain, a noteworthy distinction was observed in terms of the enhancement of energy, sleep, and emotional response. When it came to enhancing these components of QoL, AMY and DUL outperformed PGN. Measures of quality of life are becoming more widely acknowledged as significant results in the evaluation of chronic illnesses. Such data would be helpful in enabling treatment plans to target specific parts of compromised health. Therefore, in DPN patients with concurrent depression symptoms, AMY or DUL may be preferable.

None of the three medications were stopped due to intolerability; instead, they were all well tolerated. Twenty patients experienced adverse reactions from AMY; the incidence rate was 80%. This was similar to earlier research that found a 70–80% average prevalence of negative consequences. [21,22] With a 56% frequency, 14 patients experienced side effects in the DUL arm. The incidence of DUL's negative effects was also 60–65% according to earlier studies. [14,15] Seventy-six percent of individuals in the PGN arm reported experiencing adverse effects. The earlier research likewise revealed a 75–80% rate of unfavorable outcomes. [17–20]

Although the median doses of all three medications were lower in our study than in the prior studies, the similar prevalence of adverse effects among study participants may indicate that our population is more sensitive to these treatments, supporting the treating physicians' observations. The most frequent side effects, which were observed in all three groups, were sedation and vertigo. Those receiving PGN treatment experienced the lowest incidence of sedation when compared to the other two groups. There were no unanticipated or severe ADRs in our investigation, and all ADRs were linked to the medication's mode of action.

Our study strength was that it evaluated the three medications' safety and efficacy in a real-world clinical setting. Nevertheless, it had certain drawbacks, such as being an observational study with a small sample size and a brief follow-up. Furthermore, we haven't evaluated how the individuals' altered glycemic status has affected the intensity of their DPN pain. This study did not evaluate other known causes of neuropathy, such as uremia, vitamin deficiencies, smoking, and genetic factors.

Conclusion

For DPN patients, AMY, DUL, and PGN are just as safe and effective as first-line medications for treating pain symptoms. PGN improved QOL less than AMY or DUL, although it had a decreased likelihood of sedation.

To properly evaluate the efficacy and safety of medications for DPN, more research in the Indian population is needed, preferably with a bigger sample size and a longer follow-up period.

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