

Amitriptyline Vs Pregabalin in Painful Diabetic Neuropathy A Randomised Placebo-Based Study

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ABSTRACT

Aim: To compare the efficacy of amitriptyline, pregabalin and placebo in alleviating pain associated with diabetic peripheral neuropathy.

Method: A total of 150 patients were randomly recruited for the study. Assessment for pain relief was carried out on an 11-point, Likert-like numeric rating scale [NRS; 0= no pain” to 10=worst possible pain”) over a 7-day baseline period. Following a 1-week washout period without study medications, the participants were divided into 3 groups, each consisting of 70 patients, receiving either placebo, amitriptyline or pregabalin for a period of 6-week. The initial doses of pregabalin and amitriptyline were 75 mg twice daily and 10 mg at bedtime, respectively. Doses were titrated upward as necessary during weeks 1 and 3 of therapy. The maximum doses of pregabalin and amitriptyline were 300 mg twice daily and 75 mg at bedtime, respectively. Responders were patients who experienced 50% or more reduction in the baseline pain score on NRS.

Results: 210 patients were included in the study. 126(60%) were males and 84 (40%) were females. The age ranged from 22 to 76 years. 112(53.3%) had diabetes of <15 years duration, while the rest 98 (46.7%) had been suffering from DM for >15 years. 105 (50%) suffered from diabetic neuropathy for a duration <6 months, while the rest 50% had painful DN for a period exceeding 6 months.

Significant improvement in pain of DPN was observed in patients receiving pregabalin (48.1%) and amitriptyline (41.4%) as compared to the ones getting placebo (10.5%)

Conclusion: treating patients of DPN with pregabalin and amitriptyline results in better improvement in pain as compared to placebo. Out of the two drugs, pregabalin demonstrated greater response.

Key words: diabetic poly neuropathy (DPN), numeric rating scale (NRS)

INTRODUCTION

The prevalence of diabetic neuropathy is as high as 50% in patients who have had diabetes for 25 years¹ and painful diabetic peripheral neuropathy (DPN) occurs in up to 26% of all persons with diabetes². Symptoms range from mild dysesthesias to severe unremitting pain^{3,4}. As patients mostly suffer from symptoms on a daily basis, painful DPN has a major negative impact on the quality of life^{3,4}. Medications of several different classes are used to treat painful DPN with varying degrees of efficacy, safety and tolerability. Clinical trials confirm the efficacy of both antidepressants and anticonvulsants for the treatment of painful diabetic neuropathy. Many randomized controlled trials have demonstrated the efficacy of tricyclic antidepressants such as amitriptyline in painful DPN^{5,6}. The antiepileptic agents, gabapentin and pregabalin have also recently attained widespread usage in the treatment of painful DPN. These agents bind to the auxiliary $\alpha 2-\delta$ subunit of the voltage sensitive calcium channel thereby

decreasing Ca^{2+} influx at nerve terminals and modulating neurotransmitter release⁷. The aim of this study was to compare the efficacy of amitriptyline, pregabalin and placebo in alleviating pain associated with diabetic peripheral neuropathy.

MATERIALS AND METHOD

The study was carried out in the medicine department of two tertiary care hospitals, Mayo Hospital and Services Hospital, Lahore. A total of 150 patients were randomly recruited for the study. Patients with the following criteria were included in the study: age ≥ 18 years age, DPN for at least 6 months duration, an average pain score ≥ 4 (on an 11-point, Likert-like numeric rating scale [NRS]; 0=“no pain” to 10=“worst possible pain”) over a 7-day baseline period. Exclusion criteria were: pain not associated with DPN, mononeuropathies or proximal neuropathies, prior therapeutic failure with any antidepressant or anticonvulsant therapy. Informed consent was taken from all patients provided before participation. All participants underwent a 1-week washout period without study medications. The participants were divided into 3 groups, each consisting of 70 patients, receiving either placebo,

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amitriptyline or pregabalin for a period of 6-week. Active treatments were titrated upward as necessary during weeks 1 and 3 of therapy. The initial doses of pregabalin and amitriptyline were 75mg twice daily and 10 mg at bedtime, respectively. The maximum doses of pregabalin and amitriptyline were 300mg twice daily and 75 mg at bedtime, respectively. The primary study outcome was reduction in pain; responders were patients who experienced 50% or more reduction in the baseline pain score on NRS.

The data was analysed using SPSS version 19 for Windows by applying descriptive statistics and cross tabulation. Frequency and percentages were calculated. Chi-square test was used for qualitative variables and the t-test was used for comparing means. Significance was kept at p-value less than 0.05.

RESULTS

A total of 210 patients were included in the study. 126(60%) were males and 84 (40%) were females. The age ranged from 22 to 76 years. 112(53.3%) had diabetes of <15 years duration, while the rest 98 (46.7%) had been suffering from DM for >15 years. 105 (50%) suffered from diabetic neuropathy for a duration <6 months, while the rest 50% had painful DN for a period exceeding 6 months. The response to therapy was measured in terms of point reduction in NRS at the end of 6 weeks. Significant improvement in pain of DPN was observed in patients receiving pregabalin (48.1%) and amitriptyline (41.4%) as compared to the ones getting placebo (10.5%) (Chart 1). Amongst those getting the drugs, 9(12.8%) patients demonstrated a better response with pregabalin than amitriptyline (Table 1).

Chart 1: Comparison of response to therapy

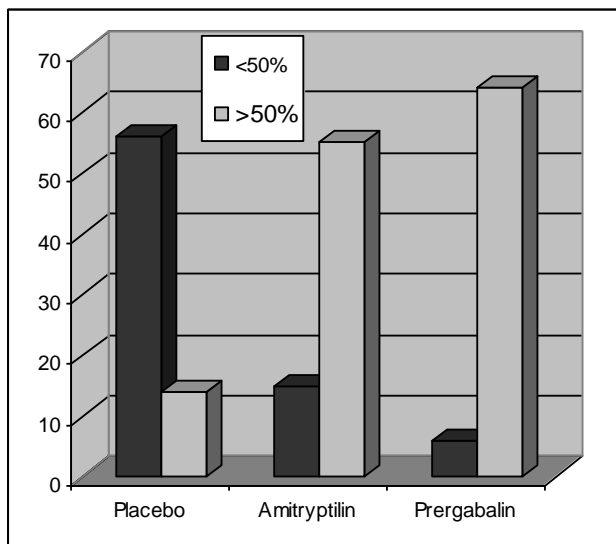


Table 1: Comparison of response to therapy in various groups

Therapy	Response		Total
	<50%	>50%	
Placebo	56	14	70
Amitriptyline	15	55	70
Pregabalin	6	64	70
Total	77	133	210

It was observed that the response to either drug was significantly better with those (80) with shorter duration of DPN i.e., <6 months as compared with those (53) who have a longer duration of DPN (Table 2)

Table 2: Effect of duration of neuropathy on the response to therapy

Therapy	Duration of neuropathy	Response		Total
		<50%	>50%	
Placebo	<6mns	21	7	28
	>6mns	35	7	42
	Total	56	14	70
Amitriptyline	<6mns	1	34	35
	>6mns	14	21	35
	Total	15	55	70
Pregabalin	<6mns	3	39	42
	>6mns	3	25	28
	Total	6	64	70
Total	<6mns	25	80	105
	>6mns	52	53	105
	Total	77	133	210

DISCUSSION

The main findings of this study are:

1. Patients of painful DPN receiving either pregabalin or amitriptyline showed statistically significant improvement at the end of 6 weeks as compared to placebo.
2. More improvement was observed in patients receiving pregabalin than amitriptyline.

The results of the current trial echo those of some previous randomized study comparing antidepressants and anticonvulsants with placebo and each other in the treatment of painful diabetic neuropathy, where either drug proves effective in at least a short term relief of pain.^{8,9,10,11} Bansal et al demonstrated in a trial comparing amitriptyline and pregabalin that there are few differences between the two treatments in efficacy, though pregabalin might be the alternative choice as it is associated with fewer adverse effects in our population¹². In our study pregabalin showed some advantage over amitriptyline in improving pain of DPN. Another observation in the study was presence of factors which interfered with clinical improvement of patients in the study groups, including longer duration and

poorly controlled diabetes mellitus, and a longer duration of DPN .

The results of this study can leave the clinician in a conundrum: what exactly is the best treatment for painful diabetic neuropathy? It can be concluded that as multiple treatments are effective for the management of diabetic peripheral neuropathy, therefore individual patient factors and preferences are critical in the decision of which treatment to choose. A major factor in this decision for many patients is the profound difference in price between medications such as pregabalin and amitriptyline. Given the average dosages used in the current study, treatment with pregabalin could cost much more than treatment with amitriptyline . However, the lower cost of amitriptyline must be weighed against its more significant profile of adverse events especially in elderly patients. Such events include a higher risk of falling as well as life-threatening arrhythmias.

CONCLUSION

Although an increasing number of trials have investigated different kinds of drugs to manage neuropathic pain, anticonvulsants and antidepressants are still the options most commonly used for painful diabetic neuropathy. Long term studies of the efficacy and adverse effects of anticonvulsants and antidepressants are needed, as these drugs are commonly used in clinical setting. Further studies are needed on ion channel blockers, N-methyl-D-aspartate antagonists, and opioids, as well as non-pharmacological strategies.

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