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Original Research Article

Pregabalin versus Gabapentin in the Management of Painful Diabetic Neuropathy

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Abstract: Diabetic neuropathy develops in the majority of poorly controlled diabetic patients as a late complication. Painful diabetic neuropathy represents a major health problem as it may present with excruciating neuropathic pain and is responsible for substantial morbidity, increased mortality and impaired quality of life. The aim is to compare the efficacy of Pregabalin and Gabapentin in painful diabetic neuropathy. This study was conducted on 100 diagnosed patients of diabetes with painful diabetic neuropathy presenting in the department of Medicine of a tertiary care teaching hospital of Punjab, India. Patients were divided in two groups of 50 each. Pregabalin (150-300 mg/day) was administered to group I and Gabapentin (300-2400 mg/day) to group II for 6 weeks. Follow up assessment of various clinical parameters was done at weekly intervals while Visual Analogue Scale (VAS) Score and Likert Scale Score assessments were done at 2, 4 and 6 weeks of treatment. Overall, it was observed that both Pregabalin and Gabapentin showed an improvement in VAS score and Likert scale score, but the improvement was significantly more with Pregabalin than Gabapentin. In this study, Pregabalin was clearly superior to Gabapentin in the improvement of parameters like spontaneous pain, burning sensation and numbness. This study concluded that it is important to treat patients with painful diabetic neuropathy with tailor-made approach. Monotherapy with Pregabalin or Gabapentin produced clinically meaningful pain relief however; pain reduction was superior with Pregabalin compared to Gabapentin. Therefore, it is suggested that Pregabalin could be a better therapeutic option in patients with painful diabetic neuropathy.
Keywords: diabetes, painful, neuropathy, Pregabalin, Gabapentin

Key Messages: Early identification and treatment of painful diabetic neuropathy is of utmost importance to prevent significant morbidity associated with it. Besides good glycemic control, both Pregabalin and Gabapentin produce clinically meaningful pain relief; however pain reduction is superior with Pregabalin as compared to Gabapentin. In the face of recent advances in treatment modalities, the future prospective management of diabetic neuropathy appears bright and convincing.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia together with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both. DM is associated with wide spectrum of neuropathic syndromes. The diabetic neuropathies are heterogeneous in nature, ranging from a mild asymptomatic distal sensory neuropathy to a severe disabling radiculoplexus neuropathy.

Diabetic neuropathy is the most common complication of long standing DM and through its much feared sequel, the diabetic foot, is responsible for most diabetes related hospitalization [1]. It is estimated that at least 20% of adults with diabetes have at least one manifestation of diabetic neuropathy. Most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy and autonomic neuropathies. Diabetic peripheral neuropathic pain (DPNP) affects approximately 11% of patients with diabetic peripheral

neuropathy (DPN). Neuropathic pain may be stimulus evoked (e.g., allodynia) or stimulus-independent (spontaneous) pain that may be continuous or intermittent. Spontaneous pain often is paroxysmal and described by patients as shooting, stabbing or electric in nature [2]. Neuropathic pain has been associated with impaired quality of life, reduced individual productivity and increased patient and healthcare resource expenditure [3, 4]. Co-morbid conditions include sleep disturbances, depression and anxiety disorders [4], increasing even further the economic burden to the healthcare system.

Several mechanisms may be responsible for the development of DPN [5, 6]. They include microangiopathy with endoneural hypoxia, excessive oxidative stress with overproduction of harmful reactive oxygen species, defect in macrophage function and inflammatory repair, reduced regenerative activity of Schwann cells and impaired neuronal cell body response caused by deficient neurotropic support [6].

Therapeutic options for diabetic neuropathy [7] include treatment of hyperglycemia, tricyclic and other anti-depressants (e.g. Amitriptyline, Nortriptyline, Desipramine, Venlafaxine, Duloxitene), anti-convulsants (e.g. Pregabalin, Gabapentin, Carbamazepine, Phenytoin, Lamotrigine, Topiramate), antiarrythmics (e.g. Mexiletine), Aldose Reductase inhibitors (e.g. Epalrestat, Ranirestat, Fidarestat, Zenarestat, Tolrestat, Zopolrestat), α-lipoic acid, Methylcobalamin, Nerve Growth Factors (Neurotrophins), Protein kinase C β inhibitor (Roboxistaurin), topical agents (Capsaicin) and Transcutaneous Electrical Nerve Stimulation (TENS).

Both Pregabalin and Gabapentin share similar mechanism of action such as binding to calcium channel and modulating calcium influx as well as influencing GABAnergic neurotransmission [8]. The recommended starting dosage of Pregabalin is 150 mg/day, taken in two or three divided doses. Based on individual patient response and tolerability, the dose may be gradually increased, to a maximum of 600 mg/day. Clinical trials using Pregabalin for both peripheral and central neuropathic pain, showed a reduction in pain scores within the first week, which was maintained throughout the treatment period [9, 10]. Alternatively, the starting dose of gabapentin is 900 mg/day given as three equally divided doses, increasing gradually up to a maximum daily dose of 3,600 mg.

Painful diabetic neuropathy represents a major health problem and its management remains a challenge for the physicians. The present study was planned to compare the efficacy of two commonly used drugs, Pregabalin and Gabapentin, in the management of painful diabetic neuropathy so as to facilitate decision-making in providing the best therapeutic option for this condition.

MATERIAL AND METHODS

This study was conducted in the department of Medicine of a tertiary care teaching hospital of Punjab, India. It was a prospective randomized single blind parallel group single center observational study of 100 diagnosed patients of diabetes with painful diabetic neuropathy admitted in the medical wards or attending the out-patient department. The study was conducted after obtaining the permission of the institutional ethics committee. Written informed consent was taken from each subject before enrolling him/her for the study. The data was collected by the first author as per the detailed questionnaire. Following detailed history and thorough clinical examination, necessary investigations were undertaken in all the patients like hemoglobin, total leucocyte count (TLC), differential leucocyte count (DLC), fasting blood sugar, post prandial blood sugar, renal function tests, liver function tests, Chest X-ray and electrocardiograph (ECG).

Following two groups were compared in this study:

- Group I: Comprised of 50 cases, which were given Pregabalin, starting with 75 mg twice daily. Dose was titrated up to a maximum of 300 mg/day according to improvement of pain, side effects and patient compliance.

- Group II: Comprised of 50 cases, which were given Gabapentin, starting with 300 mg once daily. Dose was titrated up to a maximum of 2400 mg/day according to improvement of pain, side effects and patient compliance.

Patients were followed at weekly intervals for 6 weeks. Patients not improving with Pregabalin or Gabapentin were excluded from the study.

Inclusion Criteria

1. Diagnosed patients of DM (controlled or uncontrolled) with clinical signs and symptoms suggestive of painful diabetic neuropathy.

Exclusion Criteria

1. Patients with DM having any other disease known to cause peripheral neuropathy like chronic kidney disease, liver failure, post herpetic neuralgia, etc.
2. Patients with DM on drugs known to cause peripheral neuropathy like Isoniazid, Phenytoin, Amiodarone, Nitrofurantoin, etc.
3. Patients with DM with history of chronic alcoholism.
4. Patients of peripheral diabetic neuropathy having pain intensity of VAS score < 40 mm or Likert scale score < 4.
5. Patients with altered sensorium or disturbed

mental state or uncooperative patients.

Assessment of Diabetic Neuropathy:

Both subjective and objective assessments were undertaken.

(A) Subjective: For painful diabetic neuropathy assessment, the following pain scales were used:

1. Visual Analogue Scale (VAS): VAS is a scale 100 mm long with 1 mm markings, marked from 0 to 100. Patients mark the point on the scale that they feel represents their pain perception.
2. Likert Scale: It is an 11 points symptoms severity scale; 0: no symptoms, 1-3: mild symptoms, 4-6: moderate symptoms, 7-9: severe symptoms, 10: worst imaginable symptoms.

Only patients with > 40 mm pain intensity measurement on VAS scale and > 4 point score on Likert scale were included in this study.

(B) Objective: Quantitative Sensory Testing (QST) was used as objective method for assessment of diabetic neuropathy. Sensations were measured on a three-point scale (0-absent, 1-reduced, and 2-normal) for the following parameters in the hands and the feet: vibration perception examined with a 128 Hz tuning fork, pain sensation with a disposable pin, light touch with Semmes Weinstein monofilament, joint position on the fingers and the toes, and thermal sensation with thermo test tubes containing hot and cold water.

RESULTS

In this study of 100 patients with 50 patients in each Pregabalin and Gabapentin group, both male to female ratio (1 and 0.9 respectively) and the mean age of patients in the two groups were comparable (56.84 ± 6.48 years and 57.24 ± 6.34 years respectively).

All the 50 cases in both the groups had burning sensation at baseline. At the end of treatment, i.e. 6 weeks, there was significantly more improvement in the Pregabalin group with 24 patients recovered from burning sensation (48%) compared to the Gabapentin group, where only 18 patients recovered from burning sensation (36%) (Table 1).

Table 1: Effect on burning sensation

Duration in weeks	Study population with burning sensation			
	Pregabalin (n=50)		Gabapentin(n=50)	
	No. of cases	%	No. of cases	%
Baseline	50	100.0	50	100.0
1 week	48	96.0	50	100.0
2 weeks	45	90.0	49	98.0
3 weeks	42	84.0	46	92.3
4 weeks	38	76.0	42	84.0
5 weeks	33	66.0	37	74.0
6 weeks	26	52.0	32	64.0

In each group, 38 patients (76%) had spontaneous pain at baseline. However, after 6 weeks treatment, the Pregabalin group showed a significant improvement in symptoms in 12 patients (31.57%) as compared to the Gabapentin group in which only 7 patients got relief (18.42%) at the end of 6th week (Table 2).

Table 2: Effect on spontaneous pain

Duration in weeks	Study population with spontaneous pain			
	Pregabalin(n=50)		Gabapentin(n=50)	
	No. of cases	%	No. of cases	%
Baseline	38	76.0	38	76.0
1 week	37	74.0	38	76.0
2 weeks	36	72.0	37	74.0
3 weeks	33	66.0	36	72.0
4 weeks	31	62.0	34	68.0
5 weeks	28	56.0	33	66.0
6 weeks	26	52.0	31	62.0

In this study, 43 out of 50 patients in Pregabalin group (86%) and 42 out of 50 patients in Gabapentin group (84%) had numbness at baseline. After 6 weeks, the proportion of cases with numbness had significantly fallen from baseline in both the groups and the efficacy in Pregabalin group was better where 23 patients recovered (53.5%) in comparison to Gabapentin group where only 14 patients (33.5%) got relief from numbness. All the 100 cases from both the groups showed absent to reduced sensation at baseline. After 6 weeks treatment, significantly more number of cases i.e. 11 patients (22%) from the Pregabalin group had normal sensation as compared to the Gabapentin group,

in which 6 patients (12%) regained normal sensation (Table 3).

Table 3: Effect on sensation

Duration in weeks	Sensation in study population					
	Pregabalin			Gabapentin		
	Absent	Reduced	Normal	Absent	Reduced	Normal
Baseline	24(48.0%)	26(52.0%)	-	23(46.0%)	27(54.0%)	-
1 week	23(46.0%)	27(54.0%)	-	22(44.0%)	28(56.0%)	-
2 weeks	21(42.0%)	27(54.0%)	2(04.0%)	20(40.0%)	29(58.0%)	1(02.0%)
3 weeks	18(36.0%)	28(56.0%)	4(08.0%)	19(38.0%)	30(60.0%)	1(02.0%)
4 weeks	15(30.0%)	30(60.0%)	5(10.0%)	16(32.0%)	32(64.0%)	2(04.0%)
5 weeks	11(22.0%)	31(62.0%)	8(16.0%)	13(26.0%)	33(66.0%)	4(08.0%)
6 weeks	7(14.0%)	32(64.0%)	11(22.0%)	9 (18.0%)	35(70.0%)	6(12.0%)

In this study, both the groups were comparable in terms of severity of pain at baseline and there was no statistically significant difference ($p>0.05$) in the mean value of VAS score at baseline, which was 86.44 ± 2.79 mm and 86.64 ± 2.80 mm respectively in the right and left foot in the Pregabalin group and 86.60 ± 3.56 mm and 86.62 ± 3.57 mm respectively in the right and left foot in the Gabapentin group. However, it was seen that at the end of 6 weeks, there was statistically significant difference ($p<0.05$) in its mean value in the two study groups; the VAS score at the end of 6 weeks in the right and left foot was 38.90 ± 5.70 mm and 38.96 ± 5.54 mm respectively in the Pregabalin group and 41.62 ± 4.79 mm and 41.62 ± 4.89 mm respectively for the Gabapentin group. The mean improvement in VAS Score after 6 weeks of treatment with Pregabalin was 47.54 ± 4.94 mm in right foot & 47.68 ± 4.97 mm in left foot; and the mean improvement in VAS Score after 6 weeks of treatment with Gabapentin was 44.98 ± 4.46 mm in right foot & 45.00 ± 4.54 mm in left foot. So, the improvement in VAS Score was significantly ($p<0.01$) more in Pregabalin group as compared to Gabapentin group (Table 4).

Table 4: Comparison of VAS Scores between two groups

VAS Score	Pregabalin		Gabapentin	
	Right foot	Left foot	Right foot	Left foot
Baseline	86.44 ± 2.79 mm	86.64 ± 2.80 mm	86.60 ± 3.56 mm	86.62 ± 3.57 mm
At 6 Weeks	38.90 ± 5.70 mm	38.96 ± 5.54 mm	41.62 ± 4.79 mm	41.62 ± 4.89 mm
Mean improvement	47.54 ± 4.94 mm	47.68 ± 4.97 mm	44.98 ± 4.46 mm	45.00 ± 4.54 mm

Mean value of Likert scale scores also showed no statistically significant difference ($p>0.05$) at baseline in the two study groups, which was 7.70 ± 0.83 and 7.78 ± 0.86 respectively in the right and left foot in the Pregabalin group and 7.86 ± 0.78 and 7.86 ± 0.89 respectively in the right and left foot in the Gabapentin group. However, at the end of 6 weeks, there was statistically significant difference ($p<0.01$) in the mean value of Likert scale scores in the two study groups, with 2.78 ± 0.58 and 2.68 ± 0.55 in the right and left foot respectively in the Pregabalin group and 4.44 ± 0.61 and 4.34 ± 0.65 in the right and left foot respectively in the Gabapentin group. The mean improvement in Likert scale score after 6 weeks of treatment with Pregabalin was 4.92 ± 0.94 in right foot & 5.10 ± 0.86 in left foot; and the mean improvement in Likert scale score after 6 weeks of treatment with Gabapentin was 3.42 ± 0.64 in right foot & 3.34 ± 0.65 in left foot.. So in this study, at the end of 6 weeks, the improvement in Likert Scale Score was significantly ($p<0.01$) more in Pregabalin group as compared to Gabapentin group (Table 5).

Table 5: Comparison of Likert Scale Scores between two groups

Likert Scale Score	Pregabalin		Gabapentin	
	Right foot	Left foot	Right foot	Left foot
Baseline	7.70 ± 0.83	7.78 ± 0.86	7.86 ± 0.78	7.86 ± 0.89
6 Weeks	2.78 ± 0.58	2.68 ± 0.55	4.44 ± 0.61	4.34 ± 0.65
Mean improvement	4.92 ± 0.94	5.10 ± 0.86	3.42 ± 0.64	3.34 ± 0.65

DISCUSSION

Neuropathic pain carries a great disease burden for patients and, is also associated with a significant economic burden. There are a limited number of direct head-to-head comparison studies reported for drugs used in the treatment of painful diabetic neuropathy. In the present study, the efficacy of Pregabalin and Gabapentin was compared in patients with painful diabetic neuropathy. Both the drugs were administered for 6 weeks and their effects on pain and other parameters like burning sensation and numbness were

evaluated. Pain intensity was evaluated using VAS and Likert scale scores.

Effect on burning sensation:

At the end of 6 weeks treatment, more patients in the Pregabalin group (48%) recovered from burning sensation as compared to the Gabapentin group (36%).

Effect on spontaneous pain:

Pregabalin was found to be superior to Gabapentin in providing relief from spontaneous pain as more patients in the Pregabalin group showed improvement in their symptoms (31.57%) at the end of 6 weeks as compared to those in the Gabapentin group (18.42%).

Effect on numbness:

Pregabalin was also found to be more effective than Gabapentin in reducing numbness. At the end of 6 weeks, 53.5% patients in the Pregabalin group recovered from numbness as compared to Gabapentin group where only 33.3% patients got relief from numbness.

Effect on sensations:

Objective assessment of sensations also revealed superiority of Pregabalin over Gabapentin. After 6 weeks therapy, significantly more (22%) number of cases from the Pregabalin group had normal sensation as compared to those in the Gabapentin group (12%).

Effect on VAS and Likert Scale Scores:

VAS score was measured for all the patients in both the groups at baseline and there was no statistically significant difference ($p>0.05$) in the mean value of VAS Score at baseline in the two study groups. At the end of 6 weeks, both the groups demonstrated a decrease in the VAS scores, however, there was statistically significant difference ($p<0.05$) in the mean value of VAS Score in the two study groups. The improvement in VAS Score was significantly ($p<0.01$) more in the Pregabalin group as compared to the Gabapentin group. Similar trend was noted with the Likert scale scores. At the end of 6 weeks, the improvement in Likert scale score was significantly ($p<0.01$) more in the Pregabalin group as compared to the Gabapentin group.

Thus, both drugs showed an improvement in VAS score and Likert scale score which suggests that both drugs are effective in painful diabetic neuropathy. But, in comparison to Gabapentin, Pregabalin resulted in more improvement in the VAS score and Likert scale score. This is further supported by the improvement in subjective symptoms (spontaneous pain, numbness and burning sensation).

Richter *et al.;* [11] in their study observed that Pregabalin 300mg/day provided greater than 50% reduction in mean pain score from baseline in 40% of patients. Rosenstock J *et al.;* [12] also reported improvement in mean neuropathic score in 67% of Pregabalin treated patients. Similar results were observed by Lesser *et al.;* [13].

In seven double-blind, randomized, placebo-controlled trials using Pregabalin to treat painful DPN with dosages of 150, 300, and 600 mg/d, administered over a duration of 5-13 weeks, it has been shown that Pregabalin significantly reduced pain and pain-related sleep interference associated with DPN [14].

Backjona *et al.;* [15] in their study of 165 diabetic patients reported a significant decrease in the mean pain score from 6.4 on Likert scale at baseline to 3.9 after 12 weeks of therapy with Gabapentin compared to placebo (from 6.5 to 5.1). Gabapentin-treated subjects also demonstrated statistically significant ($p<0.05$) benefits as depicted using sleep interference scores, total pain quality scores, quality of life scores and mood assessments.

Toth *et al.;* [16] in their study substituted Gabapentin with Pregabalin in patients with diabetic peripheral neuropathy. Results showed that both previous responders and non-responders to gabapentin had additional pain relief of approximately 25% after initiation of Pregabalin. Another study by Tarride *et al.;* showed that 12 weeks therapy with Pregabalin was associated with nine additional days with no or mild pain, against six additional days with Gabapentin therapy [16].

Athanasakis *et al.;* in their study compared Pregabalin with Gabapentin in the management of peripheral neuropathic pain associated with diabetic neuropathy. Mean pretreatment pain scores were identical (6.9) for both Pregabalin and Gabapentin. Post-treatment pain score mean values were 4.1 for Pregabalin and 4.8 for Gabapentin which was statistically significant. Pregabalin also demonstrated a statistically significant reduction in days with moderate to severe pain when compared to Gabapentin [17].

Rodriquez *et al.;* [3] in their study also supported the superiority of Pregabalin over Gabapentin in painful diabetic neuropathy. They reported that as compared to Gabapentin, Pregabalin yielded an estimated mean of 8 additional days with no or mild pain, 6 days with ≥30% reduction in pain intensity, 9 days with ≥50% reduction in pain intensity, and a gain of 0.1186 quality-adjusted life-years (QALYs).

Limitations in our study:

I) This was an open label design.
II) Sample size was small.
III) Follow-up of patients was only for 6 weeks and therefore, the long term efficacy and safety of the study drugs could not be assessed.

CONCLUSION:

Diabetic neuropathy develops in the majority of poorly controlled diabetic patients as a late

complication. Treatment is of utmost importance as it accounts for significant morbidity and economic burden. 60-70 percent of these patients may progress to even serious complications like diabetic foot and amputation. The treatment of diabetic neuropathy includes symptomatic relief of complications besides good glycemic control.

In the present study both Pregabalin and Gabapentin showed an improvement in VAS score and Likert scale score, but the improvement was significantly more with Pregabalin than Gabapentin. In this study, Pregabalin was clearly ahead of Gabapentin in efficacy parameters like improvement in spontaneous pain, burning sensation and numbness.

So, from the present study we conclude that monotherapy with Pregabalin or Gabapentin produces clinically meaningful pain relief in patients with painful diabetic neuropathy and pain reduction is superior with Pregabalin compared to Gabapentin. Therefore, it is suggested that these findings should be considered in the decision-making process when choosing the therapeutic option for the treatment of diabetic neuropathic pain. However, further studies in larger number of patients and for longer duration are necessary to confirm the benefits of Pregabalin over Gabapentin.

REFERENCES

1. Vinik AI. Diabetic neuropathies. In Controversies in Treating Diabetes 2008 (pp. 135-156). Humana Press.
2. Brown MJ, Bird SJ, Watling S, Kaleta H, Hayes L, Eckert S, Foyt HL. Natural progression of diabetic peripheral neuropathy in the Zenarestat study population. Diabetes Care. 2004 May 1; 27(5):1153-9.
3. Rodriguez MJ, Diaz S, Vera-Llonch M, Dukes E, Rejas J. Cost-effectiveness analysis of pregabalin versus gabapentin in the management of neuropathic pain due to diabetic polyneuropathy or post-herpetic neuralgia. Current medical research and opinion. 2007 Oct 1; 23(10):2585-96.
4. Navarro A, Saldaña MT, Pérez C, Torrades S, Rejas J. A cost-consequences analysis of the effect of pregabalin in the treatment of peripheral neuropathic pain in routine medical practice in primary care settings. BMC neurology. 2011 Jan 20; 11(1):1.
5. Yasuda H, Terada M, Maeda K, Kogawa S, Sanada M, Haneda M, Kashiwagi A, Kikkawa R. Diabetic neuropathy and nerve regeneration. Progress in neurobiology. 2003 Mar 31; 69(4):229-85.
6. Kennedy JM, Zochodne DW. Impaired peripheral nerve regeneration in diabetes mellitus. Journal of the Peripheral Nervous System. 2005 Jun 1; 10(2):144-57.
7. Freeman R. The Nervous System and Diabetes. In Joslin's Diabetes Mellitus, 14th Edition, Kahn CR, Weir GC, King GL, Moses AC, Smith RJ, Jacobson AM editors, Lippincott Williams & Wilkins, Boston, 2004: 958-60.
8. Belliotti TR, Capiris T, Ekhato IV, Kinsora JJ, Field MJ, Heffner TG, Meltzer LT, Schwarz JB, Taylor CP, Thorpe AJ, Vartanian MG. Structure-activity relationships of pregabalin and analogues that target the α2-δ protein. Journal of medicinal chemistry. 2005 Apr 7; 48(7):2294-307.
9. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible-and fixed-dose regimens. Pain. 2005 Jun 30; 115(3):254-63.
10. Strojek K, Flöter T, Balkenohl M, Xie F, Griesing T. Novel therapeutic agents: Pregabalin in the management of chronic neuropathic pain (NEP): A novel evaluation of flexible and fixed dosing. The Journal of Pain. 2004 Apr 30; 5(3):S59.
11. Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. The journal of pain. 2005 Apr 30; 6(4):253-60.
12. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004 Aug 31; 110(3):628-38.
13. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy A randomized controlled trial. Neurology. 2004 Dec 14; 63(11):2104-10.
14. Freeman R, Durso-DeCruz E, Emir B. Efficacy, Safety, and Tolerability of Pregabalin Treatment for Painful Diabetic Peripheral Neuropathy Findings from seven randomized, controlled trials across a range of doses. Diabetes care. 2008 Jul 1; 31(7):1448-54.
15. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E, Gabapentin Diabetic Neuropathy Study Group. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. Jama. 1998 Dec 2; 280(21):1831-6.
16. Tarride JE, Gordon A, Vera-Llonch M, Dukes E, Rousseau C. Cost-effectiveness of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: a Canadian perspective. Clinical therapeutics. 2006 Nov 30; 28(11):1922-34.
17. Athanasakis K, Petrakis I, Karampli E, Vitsou E, Lyras L, Kyriopoulos J. Pregabalin versus gabapentin in the management of peripheral neuropathic pain associated with post-herpetic neuralgia and diabetic neuropathy: a cost effectiveness analysis for the Greek healthcare setting. BMC neurology. 2013 Jun 4; 13(1):1.