WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 1895-1907. Research Article ISSN 2277– 7105

COMPARATIVE ANALYSIS OF EFFECT OF PREGABALIN, GABAPENTIN AND AMITRIPTYLINE IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY BY MICHIGAN NEUROPATHY SCREENING INSTRUMENT AND NEUROPATHY DEFICIT SCORE

Rajesh M.*[1], Mohapatra S[2], Swain TR[3] and Mallik AK[4]

[1]Assistant Professor, Department of Pharmacology, Sri Muthukumaran Medical College & Research Institute, Chennai, Tamilnadu, India.

[2]Professor & HOD, Department of Pharmacology, V.S.S. Medical College, Burla, Odisha, India.

[3]Associate Professor, Post-Graduate Department of Pharmacology, S.C.B. Medical College, Cuttack, Odisha, India.

[4]Associate Professor, Department of Neurology, S.C.B. Medical College, Cuttack, Odisha, India.

Article Received on
27 May 2015,

Revised on 22 June 2015,
Accepted on 15 July 2015

***Correspondence for Author**
Dr. Rajesh M.
Assistant Professor, Department of Pharmacology, Sri Muthukumaran Medical College & Research Institute, Chennai, Tamilnadu, India.

ABSTRACT

OBJECTIVE: Diabetic peripheral neuropathy (DPN) is the most common and distressing late complication of diabetes mellitus affecting nearly 50% of diabetic patients and treatment failure cases may develop foot ulcers and gangrene requiring amputation. DPN is responsible for 50% to 75% of non-traumatic amputations. For DPN cases anticonvulsants and antidepressant group of drugs are commonly prescribed with doubtful efficacy. Hence this study was designed to assess the efficacy of Pregabalin, Gabapentin and Amitriptyline in patients with DPN in a tertiary care hospital. **METHOD:** Diabetic peripheral neuropathy cases were diagnosed by Nerve conduction study (NCS) and data was collected in a preformed proforma. Efficacy of Pregabalin, Gabapentin and Amitriptyline was assessed by Michigan Neuropathy Screening Instrument (MNSI) and Neuropathy Deficit Score (NDS) at 0 week, 4th week and 12th week in a tertiary

care hospital. The results were analysed statistically. **RESULT:** Pregabalin (75 to 300mg per day) produced significant improvement in objective neurological scores (MNSI & NDS scores) in DPN patients at 4th week and 12th week. Gabapentin (300 to 600 mg per day) Amitriptyline (30 mg per day) did so only at 12th week. **CONCLUSION:** The effect of Pregabalin was significantly greater than Gabapentin and Amitriptyline in the management of diabetic peripheral neuropathy.

KEY WORDS: Diabetic peripheral neuropathy, MNSI, NDS, Efficacy.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is the commonest complication of DM, occurring in approximately 50% of individuals with type I & type II DM in the presence of long-standing hyperglycaemia and is associated with significant chronic morbidity due to macro vascular changes associated with long-standing hyperglycaemia. While the primary symptoms of neuropathy may be highly unpleasant, the secondary complications such as falls, foot ulcers, cardiac arrhythmias and ileus are even more serious and can lead to fractures, amputations and even death in patients with diabetes mellitus. [1] It may be symptomless in majority but serious disability can occur even in asymptomatic cases. Despite an ever-increasing mass of information from epidemiological surveys, animal investigations, therapeutic trials and ex-vivo and in-vivo studies in human diabetic nerve, the causes, management and prognosis of this complication has by far remained largely enigmatic. [2] Although anti-inflammatory drugs are the mainstay of treatment of nociceptive pain like arthritis, such agents are less effective in the treatment of neuropathy including DPN. [3] There is extensive evidence of use of two important class of drugs for the treatment of DPN, the tricyclic antidepressants and the anticonvulsants. The antidepressants though remain the first-line agents in many centres, their safety and tolerability issues need to be kept in mind while treating chronic neuropathic pain.[4] The anticonvulsants are another class of drugs which have stood the test of time in the treatment of diabetic neuropathy. Drugs that have been used are carbamazepine, phenytoin, and the newer agents like pregabalin, gabapentin, lamotrigine and topiramate. [5] The FDA has approved only two drugs for the treatment of DPN i.e. Pregabalin and Duloxetine. Selection of medication for chronic neuropathy is challenging, with individualization of doses, attention to potential adverse effects, comorbid conditions and drug interactions. [6] Hence this study was designed to assess the effect of Pregabalin, Gabapentin and

Amitriptyline in the management of Diabetic peripheral neuropathy by Michigan neuropathy screening instrument (MNSI) and neuropathy deficit score (NDS) in a tertiary care hospital.

METHOD

This is a prospective, observational study conducted in collaboration with Department of Neurology of S.C.B. Medical College and Hospital, Cuttack, a premier tertiary care Hospital in Orissa. The plan of study and the parameters studied were as follows and it was approved by the Institutional Ethics Committee of S.C.B. Medical College & Hospital, Cuttack, before the onset of the study.

Plan of Study

Objective	No of Patients	Parameter studied	Visits
Demographic profile of patients	50	Age, Sex, Body weight, Type of diabetes, Duration of diabetes	• Initial visit
Efficacy assessment	35	Michigan Neuropathy Screening Instrument, Neuropathy Deficit Score	• Initial • 4th week • 12th week

Study Site & Period: This study was conducted in the Out-Patient Department of Neurology of S.C.B. Medical College & Hospital, Cuttack, over a period of one year.

Study population: The study was conducted on patients of Diabetic Neuropathy attending the Neurology O.P.D. of S.C.B. Medical College & Hospital. The Study Protocol, Case Record Form, Informed Consent Sheet and ADR Questionnaire was prepared by the study team and approved by the Institutional Ethics Committee after which patients satisfying the following Inclusion & Exclusion Criteria were enrolled in this study.

Inclusion criteria: The diagnosed cases (by Nerve Conduction Study) of Diabetic Peripheral Neuropathy(DPN) of the lower limb, with symmetrical, mixed sensory-motor Diabetic neuropathy cases, suffering from both axonal and demyelinating neuropathy with adequate glycaemic control and those who are Committed to report for follow-up at 4th and 12th week were included in this study. DPN patients receiving Pregabalin, Gabapentin and Amitriptyline as monotherapy only were included in this study. Informed consent of patients obtained.

Exclusion criteria: The neuropathy cases of non-diabetic origin, those with associated co-morbid conditions (CVA, CHF, IHD, ESRD, Liver disease) were excluded from the study.

Study Procedure: The patients attending the Neurology O.P.D. for complaints of signs and symptoms of Peripheral Neuropathy were screened for Diabetes Mellitus and other diseases known to be causing Peripheral Neuropathy. Once the diagnosis of Diabetic Peripheral Neuropathy was confirmed by the treating clinician, the patients were questioned for their willingness to participate in the study. The patients were explained about the nature of the study and the need of their regular follow up at 4^{th} week and 12^{th} week, and to stay in contact throughout the 12 week period. They were also informed about their right to withdraw from the study at any stage. The consenting patients were enrolled into the study.

Efficacy assessment of Drugs

The study group were carefully examined for the degree and type of peripheral neuropathy using 'standard objecting scoring systems' devised for this purpose by previous workers. Two such parameters were used in each patient in this study, for the assessment of efficacy of drugs, at basal (pre-treatment) and during the 4^{th} week and 12^{th} week (post-treatment) follow up visits. These were the Michigan Neuropathy Screening Instrument (MNSI), and the Neuropathy Deficit Score (NDS).

The Michigan Neuropathy Screening Instrument (MNSI): [7] It is a Structured Objective record of physical assessment of clinical features in an individual patient, as observed by the health professional. It is a ten-point assessment that relies on clinical examination of the each feet; each point depicting presence or absence of 1). Normal appearance of the feet, 2). The presence or absence of foot ulcerations, 3). The assessment of vibratory sensation in the great toes, 4). Grading of ankle reflexes and 5). Monofilament test. ***1). Appearance of feet:*** the feet are inspected for the evidence of excessively dry skin, callous formation, fissures, frank ulceration or deformities. Deformities include flat feet, hammer toes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot) and amputation. ***2). Ulceration:*** Both the right and left feet are inspected thoroughly for the presence of any ulceration. ***3). Ankle Reflexes:*** The ankle reflexes is examined using an appropriate reflex hammer (e.g. Trommer or Queen square). The ankle reflexes is elicited in the sitting position with the foot dependent and the patient relaxed. For the reflex, the foot should be passively positioned and dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles tendon is percussed directly. If the reflex is obtained, it is graded as

present. If the reflex is absent, the patient is asked to perform the Jendrassik maneuver (i.e., hooking the fingers together and pulling). Reflexes elicited with the Jendrassik maneuver alone are designated "present with reinforcement." If the reflex is absent, even in the face of the Jendrassik maneuver, the reflex is considered absent. ***4). Vibration perception at great toe:*** Vibration sensation should be performed with the great toe unsupported. Vibration sensation

Table1. The Michigan Neuropathy Screening Instrument (MNSI)

Patient Name:

ID Number:

Date:

MICHIGAN NEUROPATHY SCREENING INSTRUMENT

Physical Assessment (To be completed by health professional)

1. Appearance of Feet

	Right	Left
a. Normal	☐ 0 Yes ☐ 1 No	Normal ☐ 0 Yes ☐ 1 No
b. If no, check all that apply:		If no, check all that apply:
Deformities	☐	Deformities ☐
Dry skin, callus	☐	Dry skin, callus ☐
Infection	☐	Infection ☐
Fissure	☐	Fissure ☐
Other	☐	Other ☐
specify:	_____	specify: _____

	Right		Left	
	Absent	Present	Absent	Present
2. Ulceration	☐ 0	☐ 1	☐ 0	☐ 1

	Right			Left		
	Present	Present/ Reinforcement	Absent	Present	Present/ Reinforcement	Absent
3. Ankle Reflexes	☐ 0	☐ 0.5	☐ 1	☐ 0	☐ 0.5	☐ 1
	Present	Decreased	Absent	Present	Decreased	Absent
4. Vibration perception at great toe	☐ 0	☐ 0.5	☐ 1	☐ 0	☐ 0.5	☐ 1
5. Monofilament	Normal ☐ 0	Reduced ☐ 0.5	Absent ☐ 1	Normal ☐ 0	Reduced ☐ 0.5	Absent ☐ 1

Signature:_____ Total Score _____ /10 Points

is tested bilaterally using a 128 Hz tuning fork placed over the dorsum of the great toe on the bony prominence of the DIP joint. Patients, whose eyes are closed, will be asked to indicate

when they can no longer sense the vibration from the vibrating tuning fork. In general, the examiner should be able to feel vibration from the hand-held tuning fork for 5 seconds longer on his distal forefinger than a normal subject can at the great toe (e.g. examiner's DIP joint of the first finger versus patient's toe). If the examiner feels vibration for 10 or more seconds on his or her finger, then vibration is considered decreased. Vibration is scored as 1) present if the examiner senses the vibration on his or her finger for < 10 seconds, 2) reduced if sensed for ≥ 10 or 3) absent (no vibration detection). ***5). Monofilament testing:*** For this examination, it is important that the patient's foot be supported (i.e., allow the sole of the foot to rest on a flat, warm surface). The filament should initially be prestressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. The filament is applied perpendicularly and briefly, (<1 second) with an even pressure. When the filament bends, the force of 10 grams has been applied. The patient, whose eyes are closed, is asked to respond yes if he/she feels the filament. Eight correct responses out of 10 applications is considered normal: one to seven correct responses indicates reduced sensation and no correct answers translates into absent sensation. A score of either 0 or 0.5 or 1 is given to the absence, reduced or presence of the clinical finding, with respect to the normal as the case may be. The total score is 10 points and higher the score, greater the degree of abnormality in the neuropathy patient (Table 1).

Neuropathy Deficit Score: [8] It is another screening instrument with scoring system to conduct objective assessment of DPN, and is used for this study. It is a method to evaluate the patient's response to different stimuli. It is 5-point scoring system which checks the parameters of vibration sense, temperature perception, pin-prick sensation and Achilles reflex. Assessment of one limb is sufficient in diabetic sensory or sensorimotor polyneuropathy, as the measurement findings are shown to be symmetrical, justifying unilateral evaluation. ***1). Vibration sense:*** The stimulus is applied using a tuning fork of 128 Hz at the apex of big toe, if the response is normal the score is 0, if the response is abnormal the score is 1. ***2). Temperature perception:*** A tuning fork dipped in a beaker containing ice, and in another beaker of warm water are touched to the foot dorsum of the patient consecutively. A normal response or an abnormal response are graded as 0 and 1 respectively. ***3). Pin-prick sense:*** A pin is pricked just proximal to the big toe nail to deform the skin, by its blunt and sharp side consecutively, if the patient can differentiate between sharp and blunt prick the score is 0, if differentiation is only minimal the score allotted is 1.

4). Achilles reflex: With a percussion hammer the Achilles tendon is percussed, if tendon reflex is absent the score is 2, if present with reinforcement the score is 1, and if normally present the score is 0. It has a total score of 5; higher the score greater the disability (Table 2).

Table 2. Neuropathy Deficit Score (NDS)

Sl no	Parameter checked	Rt	Lt	Stimulus applied	Site checked	Response	Score
1	Vibration sense	✓	✓	Tuning fork 128Hz	Apex of big toe	Normal Abnormal	0 1
2	Temp perception	✓	✓	Tuning fork with beaker of ice / warm water	Foot dorsum	Normal Abnormal	0 1
3	Pin prick	✓	✓	Pin	Proximal to big toe nail (to deform the skin)	Minimal Can differentiate sharp and blunt	1 0
4	Achilles reflex	✓	✓	Percussion	Achilles tendon	Absent Present with reinforcement Present	2 1 0

Statistical analysis

The data was entered into the SPSS 17.0 for Windows Software. The demographic variables like age, sex, duration of diabetes, were analysed by descriptive statistics, simple percentages and Chi-Square test. For comparison of pre-drug and post-drug variables within a group, the Wilcoxon Signed Rank test was used for non-normally distributed continuous data. To compare variables between the groups, the Kruskal Wallis test and Mann Whitney U test was used for determining variance in non-normally distributed continuous data.

RESULTS

A total of fifty Diabetic Peripheral Neuropathy (DPN) patients satisfied the inclusion and exclusion criteria and were recruited into the study. Their demographic profile, duration of diabetes, type of DM and their medication for DPN was studied as per the study protocol. During their initial visit, patients were sensitized to note and report any ADR occurring in their day to day life and were asked to come for follow-up at 4^{th} week and 12^{th} week for evaluation of efficacy of the drugs used in DPN by MNSI and NDS. Eight patients failed to

turn up for their 4th week visit and another 7 patients did not turn up for their 12th week visit, and hence only thirty five patients successfully completed the study.

Demographic profile of DPN patients:

Most of the patients (42%) belonged to the age-group of 50-60 years, which was significantly greater than the other age groups. The age range varied from 29-75 years with the mean age being 52.25 ± 12.34 years. There were significantly (Chi-Square value = 9.680, df = 1, P < 0.01) more number of males (72%) than females (28%). All the patients suffered from Type 2 diabetes, none were suffering from type 1 diabetes in this study. A significantly greater number of patients visiting the Neurology OPD with complaints of diabetic neuropathy were suffering from diabetes for a duration of 1-5 years (46%), followed by another 38% for 6 to 10 years. The mean duration of diabetes in the study patients was 7.84 ± 6.24 years and most of the patients were under desired glycaemic control as recommended by ADA guidelines (FBS 86%, PPBS 82% and HbA1C 76% of patients).

Efficacy assessment of drugs used in DPN

Table 3. Efficacy assessment of drugs used in DPN through evaluation of MNSI (Michigan Neuropathy Screening Instrument) score

Drug treatment group	No. of patients	Mean MNSI score ± SD at		
		0 week	4th week	12th week
Pregabalin	21	4.60 ± 0.72	2.71 ± 0.56 ***	1.52 ± 0.43 *** b
Gabapentin	9	4.11 ± 0.42	3.72 ± 0.75	2.17 ± 0.35 **
Amitriptyline	5	4.50 ± 1.00	3.60 ± 0.55	1.90 ± 0.42 *

Within groups - Wilcoxon Signed Ranks Test * P< 0.05, ** P< 0.01, *** P< 0.001

Between groups - Kruskal- Wallis Test, Mann Whitney U test b = P < 0.01

As evident in Table 3, on paired comparisons within the same group, Pregabalin produced significant improvement in the MNSI scores from basal value at 4th week and 12th week. The MNSI score at 12th week was significantly less than 4th weeks score, signifying greater improvement at 12th week than 4th week. Gabapentin and Amitriptyline produced significant improvement in this score only at 12th week, over the corresponding basal scores. On comparison between the three groups, Pregabalin produced significantly greater reduction in the MNSI score than Gabapentin and Amitriptyline at 12th week.

Table 4. Efficacy Assessment of Drugs used in DPN through evaluation of NDS (Neuropathy Deficit Score)

Drug treatment group	No. of Patients	Mean NDS score ± SD at		
		0 week	4th week	12th week
Pregabalin	21	3.43 ± 0.51	2.12 ± 0.59**	1.21 ± 0.34***b
Gabapentin	9	3.33 ± 0.50	2.67± 4.33	1.83 ± 0.43**
Amitriptyline	5	3.60 ± 0.55	2.60 ± 0.55	1.40 ± 0.55*

Within groups - Wilcoxon Signed Ranks Test : * P< 0.05, **P< 0.01, *** P< 0.001

Between groups - Kruskal-Wallis Test, Mann Whitney U test b = P< 0.01

As evident in Table 4, similar observations were also obtained with the NDS score. On paired comparisons, there occurred significant improvement in the NDS scores of DPN patients after use of Pregabalin at 4th and 12th week, compared to the basal score. In patients on Gabapentin and Amitriptyline there was no change in NDS score at 4th week in comparison to the basal, while significant improvement was observed at 12th week. In the Gabapentin treated group, the NDS score at 12th week was significantly less than 4 weeks, signifying greater improvement at 12th week over 4th week. On comparison between groups, Pregabalin produced significantly higher reduction in NDS score than Gabapentin and Amitriptyline, at 12th week.

DISCUSSION

The present study is a prospective observational study, being undertaken to assess the effect of Pregabalin, Gabapentin and Amitriptyline used in the management of Diabetic peripheral neuropathy at Neurology O.P.D. of our Hospital. Out of the various types of DPN, Distal Symmetrical Peripheral Neuropathy (DSPN) is the most common type (75%), and hence this subset of DPN patients were included in the study, for uniformity of results

Fifty patients satisfying the inclusion and exclusion criteria were included into this study at initial visit, but 15 dropped out due to unexplained causes and rest 35 completed the study. Hence, analysis of demographic data was done for 50 patients, while the efficacy analysis was done for 35 patients only. On analysis of the demographic profile of the DPN patients it was observed that most of them belonged to the age group of 50 to 60 years (42%), with the mean age being 52.25 ± 12.34 years and age range 29-75 years. This is in concurrence with other studies; in the BIRDEM study,[9] conducted at Dhaka in 2006, the mean age of DN patients was 50.8 ±10.6 years and females were significantly younger than males (48.7 vs. 53.1 years) while in another study[10] at North Central Nigeria in 2003, the mean age was

54.9±12.1 years, with an age range of 22 to 87 years. These reports substantiate the facts in literature that advanced age is a risk factor for DPN. [1] In our study majority of the patients were males (72%) and only 28% were females. Literature review reveals that DPN has a gender predilection with males suffering more than females. [11] All the patients recruited in our study suffered from type 2 diabetes, and none from type 1diabetes. The mean duration of diabetes among the study population was 7.84 ± 6.24 years, most of them suffered from diabetes for a period of 1 to 5 years (46%), while 38% suffered from diabetes for 6 to 10 years. This is similar to the findings in the BIRDEM study, [9] where the mean duration of diabetes was 7.0±1.8 years, and was similar in males and females, and in the Nigerian study,[8] it was 8.4±6.9 years.

For efficacy evaluation, standard objective neurological examination scores were used in our study, which were inexpensive, rapid and validated. A very useful tool is the Michigan Neuropathy Screening Instrument, a ten-point assessment that relies on clinical examination of the feet, the presence or absence of foot ulcerations, the assessment of vibratory sensation in the great toes, and grading of ankle reflexes. [12] Many researchers have used this tool to assess DPN. To substantiate the results another objective score, based on similar approach, the Neuropathy Deficit Score was also used. This was also used by other workers.[13]

In our study Pregabalin 75 to 300 mg/day produced significant symptomatic relief as evidenced by the decrease in the MNSI and NDS scores, as early as 4th week and also at 12th week. There was significantly greater reduction in neuropathy scores at 12th week, than at 4th week. In other studies, Pregabalin produced significant improvements in pain scores within 1 week of treatment, which persisted for 6 to 12 weeks in 4 randomized controlled trials.[14] In a randomized double blind placebo controlled parallel group multicenter 8 week trial on 146 patients receiving pregabalin 300mg/day, significant improvement of mean pain scores, mean sleep interference scores and measures of quality of life, was observed over placebo in DPN patients.[15]

Pregabalin has similar pharmacokinetic features to gabapentin, but in contrast displays linear pharmacokinetics. In our study Gabapentin in doses between 300 to 600mg per day, produced significant symptomatic relief as evidenced by the decrease in the MNSI and NDS scores, at 12th week. In a randomized trial comparing gabapentin with placebo for PDN, the rates of at least moderate improvement in pain were 60% with gabapentin while 33% with placebo.[11] In other studies, it was observed that gabapentin monotherapy appeared to be efficacious in

the treatment of DPN with significant decline in daily pain scores in the gabapentin treated patients (from 6.4 to 3.9, n=82) comparison to placebo (from 6.5 to 5.1, n=80).[16] The mechanism of action of pregabalin and gabapentin, both structurally related to GABA, might not be due to their action on GABA receptor or through their influence on uptake or breakdown of GABA. Their proposed mechanism is based on the observation that gabapentin bind to alpha to delta subunit of the voltage dependent calcium channel and modulating neurotransmission in the presynaptic dorsal horn neurons.[17]

In our study, Amitriptyline in the dose of 30 mg per day, significant symptomatic relief was observed only at 12th week and not at 4th week, as evidenced by the significant decrease in the MNSI and NDS scores only at 12th week. This could be because of the smaller number of patients treated with the drug, if the number of patients in this group would have been higher, the small decrease in the 4th week score could have reached significant limits. Since long, tricyclic anti-depressants (TCA) have been the most commonly used drugs for pain relief in diabetic peripheral neuropathy. Double blind trials of the tricyclic anti-depressants have demonstrated significant benefits in reducing pain that is burning, aching, sharp, throbbing, or stinging.[10] In a randomized study comparing amitriptyline, desipramine and fluoxetine in patients with DPN, amitriptyline improved pain in 74% of patients which was significantly more than the 48% patients who improved with fluoxetine.[16]

Gabapentin compares favourably with amitriptyline in terms of efficacy and is clearly safer. Its main side effect is sedation, it needs to be taken three times a day and may cause weight gain which may worsen diabetes. [18] A recent Canadian study evaluated cost-effectiveness of pregabalin vs. gabapentin for the treatment of painful DN, and the investigators concluded that pregabalin was more cost-effective when compared with gabapentin.[19]

CONCLUSION

Pregabalin (75 to 300mg per day) produced significant improvement in objective neurological scores (MNSI scores & NDS scores) in DPN patients at 4th week and 12th week. Gabapentin (300 to 600 mg per day) and Amitriptyline (30 mg per day) did so only at 12th week. On comparison between the three groups by MNSI and NDS score, the effect of Pregabalin at 12th week was significantly greater than Gabapentin and Amitriptyline.

ACKNOWLEDGEMENTS

The authors are thankful to all the staff of pharmacology and neurology department for their support and co-operation to complete this research project.

REFERENCES

1. Sherman AL, Echeverry D. Peripheral Neuropathy. Physical medicine and Rehabilitation, 2009; eMedicine.
2. Young RJ. The management of diabetic neuropathy(section- 12). In Pickup JC, editor. Text book of Diabetes, 2nd ed, London: 1997; 51.1-51.13.
3. Brownlee M et al. Complications of Diabetes(Chapter-32). In williams, editor.Text book of Endocrinology, 11th ed, Philadelphia: 2008; 1417-1501.
4. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol, 2003; 60: 1524-34.
5. Martha S, Nolte, Karam JH. Pancreatic Hormones & Antidiabetic drugs(Chapter-41).In Katzung BM, editor. Basic and clinical pharmacology, 11th ed, New Delhi, India: McGraw-Hill: 2010; 727-751.
6. Louis kuritzky. Managing diabetic peripheral neuropathic pain in primary care. The Journal of Family Practice, 2010; 59: s15-s22.
7. Simmons Z, Feldman EL. Update on diabetic neuropathy. Curr Opin Neurol, 2002; 15: 595-603.
8. Young MJ, McCardle JE, Randall LE, et al. Improved survival of diabetic foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk management. Diabetes Care, 2008; 31: 2143–7.
9. Morkrid K, Ali L, Hussain A. Risk factors and prevalence of diabetic peripheral neuropathy: A study of type 2 diabetic outpatients in Bangladesh. Int J Diab Dev Ctries, 2010; 30: 11-7.
10. Ugoya SO, Ugoya TA, Puepet FH, Agaba EI, Ogunniyi AO. Risk determinants of diabetic peripheral neuropathy in Jos, North-Central Nigeria.Journal of Chinease Clinical Medicine, 2008; 3(5): 285-91.
11. Aaberg ML, Burch DM, Hud ZR, et al. Gender differences in the onset of diabetic neuropathy. Journal of Diabetes and its Complications, 2008; 22(2): 83-7.
12. Simmons Z, Feldman EL. Update on diabetic neuropathy. Curr Opin Neurol, 2002; 15: 595-603.

13. Sachdev Y. Diabetic Neuropathy(Section-28.3). In Sachdev Y, editor. Clinical Endocrinology and Diabetes Mellitus, 1st ed, New Delhi, India: Jaypee: 2008, pp.1007-19.
14. Frampton JE, Scott LJ. Pregabalin: in the treatment of painful diabetic peripheral neuropathy. Drugs, 2004; 64: 2813-20.
15. 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;110: 628-38.
16. Louis kuritzky. Managing diabetic peripheral neuropathic pain in primary care. The Journal of Family Practice, 2010; 59: s15-s22.
17. Sauderk CD, Werns S, Reidenberg MM. Phenytoin in the treatment of diabetic symmetrical polyneuropathy. Clin pharmacol Ther, 1977; 22: 196-9.
18. Mcquay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. BMJ, 1995; 311: 1047-52.
19. 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. Clin Ther, 2006; 28: 1922-34.