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RESEARCH ARTICLE

Effectiveness and safety of amitriptyline, duloxetine, and pregabalin in painful diabetic neuropathy: An observational study

Suji V Sumedhan[1], Vinu Wilson[2], Manoj P[3], Rajamony P N[4]

[1]Department of Pharmacology, SUT Academy of Medical Sciences, Trivandrum, Kerala, India, [2]Department of Pharmacology, Government Medical College, Trivandrum, Kerala, India, [3]Department of Neurology, Sree Gokulam Medical College and Research Foundation, Trivandrum, Kerala, India, [4]Department of Pharmacology (Retired), Sree Gokulam Medical College and Research Foundation, Trivandrum, Kerala, India

Correspondence to: Vinu Wilson, E-mail: vinuwilson85@gmail.com

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ABSTRACT

Background: Studies comparing the real-world effectiveness, safety, and effect on quality of life (QoL) of drugs for painful diabetic peripheral neuropathy (DPN) are scarce. **Aims and Objectives:** The aim of the study was to compare effectiveness, safety and effect on QoL of amitriptyline (AMY), duloxetine (DUL) and pregabalin (PGN) in DPN. **Materials and Methods:** After ethics committee approval and informed consent, 75 outpatients (25 each) prescribed any one of above drugs were consecutively recruited in a prospective and observational study. Drug effectiveness was assessed by comparing difference in mean monthly visual analogue scale (VAS) score from baseline, obtained from pain diary. QoL was assessed by comparing total and domain-wise score on Nottingham health profile (NHP) questionnaire. Safety was assessed by comparing frequency of adverse drug reactions (ADRs). Qualitative and quantitative outcome measures were compared using Chi-square test and one-way analysis of variance, respectively. $P < 0.05$ was considered statistically significant. **Results:** The difference in mean monthly VAS scores at the end of 4, 8, and 12 weeks was similar between the three drugs. Patients on PGN had smaller beneficial effects in total as well as emotional, energy, and sleep domains of NHP compared to other drugs. Sedation and dizziness occurred with all drugs but PGN had least incidence of sedation. **Conclusion:** AMY, DUL and PGN are equally effective and safe in DPN. Although PGN did not improve QoL unlike AMY and DUL, it had lower incidence of sedation.

KEY WORDS: Amitriptyline; Duloxetine; Pregabalin; Diabetic Neuropathy; Quality of Life; Safety

INTRODUCTION

Diabetes mellitus (DM) is fast gaining the status of a potential epidemic in India, especially in states such as Kerala with highly westernized lifestyle.[1,2] One of the most debilitating microvascular complications of poorly controlled chronic DM is diabetic peripheral neuropathy (DPN).[3] DPN is defined as the presence of symptoms and signs of peripheral nerve dysfunction in a patient with DM after ruling out other causes of nerve dysfunction. DPN is the most frequent cause of non-traumatic amputation in DM patients.[3,4] Globally, the prevalence of DPN varies widely from 9.6% to 78% of DM patients in different populations.[3,4] In India, the estimated prevalence of DPN varies from 18.8% to 29.1%.[5,6] In a study from South India, 19.1% of Type 2 diabetic patients had DPN.[7] In addition to neurologic disability related to sensory loss and risk of foot ulcers and amputations, approximately 15–20% of patients have painful symptoms that limit function

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and are the strongest determinant of the reduced quality of life (QoL) in DPN.[3] Patients visit multiple departments of a hospital searching for suitable pharmacological and non-pharmacological modalities for the alleviation of pain of DPN.

Unfortunately, none of the currently available drugs cure DPN and its progression can only be halted by strict glycemic control. Therefore, patients with DPN are treated by a step-wise approach that includes control of glycemic status, education and counseling on foot care and safety measures, and symptomatic treatment of pain.[3] The therapeutic approach to pain in DPN is based on the patient's presentation and comorbidities and usually follows a trial-and-error process.[8] The United States Food and Drug Administration approved medications for the management of painful DPN includes anticonvulsants (carbamazepine, pregabalin [PGN], gabapentin, and lamotrigine), antidepressants (tricyclic antidepressants, duloxetine [DUL], and fluoxetine), opioid analgesics (morphine, tramadol, and tapentadol), and topical treatments (5% lignocaine and 8% capsaicin patches).[9] The available evidence suggests that all these drugs are almost equally efficacious and better than placebo in patients with DPN, although few high-quality comparative trials have been done between them.[8] However, none of these medications afford complete relief, even when used in approved combinations. Therefore, selection of a specific agent for painful DPN is individualized based on patient's comorbidities, drug's side effect profile, preventable drug interactions, and cost of therapy.

The three drugs highlighted by clinical treatment guidelines as first-line for pain of DPN are amitriptyline (AMY), DUL, and PGN.[3,10] Majority of the studies comparing the clinical effectiveness of these three drugs have been carried out in Western countries. Very few data are available from Asia, particularly for making therapeutic decisions in the Indian population of DPN patients.[10,11] Therefore, we conducted this observational study to assess the clinical effectiveness and safety of these three drugs in DPN, to guide physicians in choosing the right drug for the right patient.

MATERIALS AND METHODS

This analytical and observational study was approved by the Institutional Ethics Committee (IEC) vide approval no. IEC No. 15/132/12/2014 dated December 09, 2014. It was carried out in the out-patient clinic of the department of neurology of a tertiary-care teaching hospital in Southern Kerala from January 2015 to November 2016. We consecutively recruited 75 outpatients with painful DPN, aged 18 years or older, having a reported HbA1c ≤8.5% within the previous 3 months and who were prescribed AMY, DUL, or PGN by their treating neurologist. Patients in whom causes of pain other than DPN were found during evaluation were excluded from the study. Patient recruitment stopped when 25 patients each had accrued into the three treatment observation groups. Written informed consent was obtained from each patient before recruitment into the study.

Outcome Measures

1. The intensity of severity of pain was recorded using a visual analog scale (VAS) measured to the nearest millimeter. The study participants were provided a monthly pain diary containing VAS to record daily pain intensity, which was collected and replaced at monthly follow-up visits. Mean monthly VAS score was calculated at end of each month for 3 months. The change in mean monthly VAS score from baseline to 3-month post-treatment was fixed as the primary end point.
2. QOL was assessed by comparing the overall and domain-wise score on the Nottingham health profile (NHP) questionnaire.[12] The NHP is a well-validated and self-reported questionnaire assessing health-related QOL within six domains: Energy, sleep, pain, physical mobility, emotional reactions, and social isolation.[13] The questionnaire takes a few minutes to complete, requiring yes or no responses to 38 simple statements. Scores range from 0 to 100, a score of 100 indicating the presence of all the limitations listed. Interpretation of the result is done by assessing relative level affected, in which the sum of the relative weights are subtracted from 100%, giving values between 0 and 1, with 0 indicating poor and 1 good health.
3. Safety assessment: The study subjects were informed about the known adverse drug reactions (ADRs) of the drug prescribed and advised to report both known as well as any new adverse event during treatment. They were followed up monthly for a period of 3 months.

Statistical Analysis

Quantitative baseline characteristics were calculated for all the patients together and then separately for the three treatment groups and expressed as mean ± SD or median (25^{th} percentile and 75^{th} percentile) for variables following normal and non-normal distributions, respectively. Qualitative variables were expressed as counts (*n*) and frequencies (%). The baseline characteristics of the three groups were compared using student independent *t*-test or Mann–Whitney U test for quantitative variables or Chi-square test for qualitative variables. Analysis of within group change in the outcome measures was done using paired *t*-test or repeated measures analysis of variance (ANOVA) with *post hoc* pair-wise comparison. Comparison of outcome measures between the three groups was done using one-way ANOVA test. Data were analyzed using free-to-use R software. $P < 0.05$ was considered statistically significant.

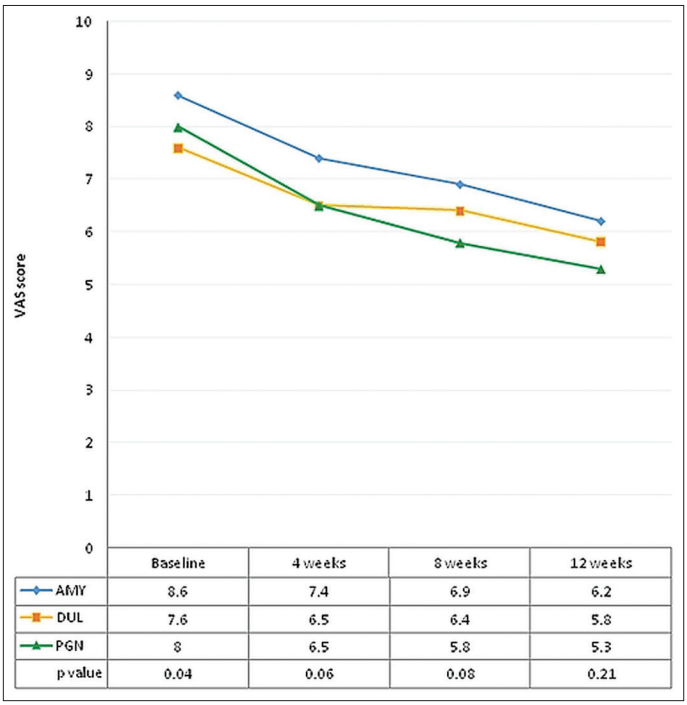
RESULTS

The patients in the three treatment groups were similar in baseline characteristics except body mass index (BMI) as

shown in Table 1. Patients who were prescribed AMY had a higher BMI at baseline compared to other two groups.

Severity of Pain

The mean VAS scores at baseline, 4, 8, and 12 weeks are shown in Figure 1. The patients in AMY group had a higher baseline VAS score compared to the other two groups ($P = 0.04$). All the three drugs produced reduction in monthly mean VAS scores over time at 4, 8, and 12 weeks compared to their respective baseline values as shown in Figure 1. However, there was no difference between the groups with respect to VAS scores at 4, 8, and 12 weeks as shown in Figure 1. The mean difference in VAS scores at the end of 4, 8, and 12 weeks from baseline between the three groups was compared as shown in Table 2. One-way ANOVA of the mean difference in VAS scores showed that there was no difference in the effectiveness of the three drugs in reducing the severity of pain over 3 months.



	Baseline	4 weeks	8 weeks	12 weeks
AMY	8.6	7.4	6.9	6.2
DUL	7.6	6.5	6.4	5.8
PGN	8	6.5	5.8	5.3
p value	0.04	0.06	0.08	0.21

Figure 1: Time series curve of mean VAS scores over 3 months

Since there was a statistically significant difference in the baseline BMI of the three groups, analysis of covariance (ANCOVA) test was done for adjusting baseline VAS scores with BMI as covariate. The means of VAS score difference in three groups were compared after adjustment for baseline BMI values [Table 3]. There was no difference between the effectiveness of the three drugs even after adjustment for baseline variability in BMI. Similarly, an ANCOVA test was also done to compare the mean monthly VAS scores after adjustment for baseline variability in VAS score. No difference in effectiveness of the three drugs was noticed even after adjusting for baseline variability in VAS scores (data not shown).

QOL

The effect of the three drugs on QOL of the patients was assessed by comparing the total as well as domain-wise scores on the NHP questionnaire at baseline and at 12 weeks as shown in Table 4. One-way ANOVA showed statistically significant difference in total score as well as components scores of energy, sleep, and emotional domains of NHP between the three groups at 12 weeks. *Post hoc* analysis showed that patients on PGN had significantly smaller beneficial effects in these domains of NHP compared to those on AMY or DUL as shown in Table 4.

Safety

A total of 53 adverse drug reactions were reported in 75 patients. All were mild, self-limiting, and did not require discontinuation of therapy. The incidence of adverse effect in each of the three treatment arms during the study period was calculated and is shown in Table 5. Sedation and dizziness, the most common adverse effects, were seen in all the three

Table 1: Baseline demographic and clinical characteristics of study participants

Baseline characteristics	Baseline values Mean±SD or median (Q1, Q3) or *n* (%)			
	AMY (*n*=25)	DUL (*n*=25)	PGN (*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
Median dose (mg)	25 (10, 25)	30 (20, 30)	75 (75, 112.5)	

*P<0.05 compared to other groups. AMY: Amitriptyline, DUL: Duloxetine, PGN: Pregabalin, BMI: Body mass index

groups. Fisher's exact test was done to see whether there is any significant difference in adverse effects between the three groups. It was found that sedation was least with PGN ($P = 0.001$) treated patients compared to the other two groups. Certain adverse effects were peculiar by their occurrence in only one treatment group. While edema occurred only in PGN group, dry mouth and urinary retention occurred in patients treated with AMY alone.

DISCUSSION

The present study showed that AMY, DUL, and PGN prescribed by the treating physicians were equally effective and safe for the symptomatic treatment of pain in DPN patients over 3 months. The three drugs produced similar reductions in subjective pain perception in patients as evidenced by comparable improvement in VAS score after adjusting for baseline differences. However, the drugs differed in the degree and domains of improvement of QOL. While both AMY and DUL improved QOL, PGN did not show similar benefit. On the other hand, though the drugs were well tolerated, PGN was associated with considerably lower incidence of sedation compared to AMY or DUL.

The primary objective of this study was to compare the real-world effectiveness of the three drugs in reducing pain severity in DPN patients. The three drugs achieved comparable reduction in pain severity over 3 months. The pain reduction as assessed by reduction in VAS score achieved with AMY was 2.32 ± 1.07, that is, ~ 23%. This is much lower as compared with pain reduction with AMY in the range of 40–50% shown in the previous studies.[14-16] However, the median dose of AMY used in our study was 25 (10, 25) mg/day, which was much lower when compared to 50–75 mg/day used in the previous studies. The pain reduction with DUL in our study was 1.88 ± 1.30, that is, ~ 19%. The previous studies which compared DUL with placebo or PGN showed a reduction in pain severity ranging from 23% to 50%.[17-19] The dose of DUL used in these studies (60 mg/day) was higher compared to our median dose of 30 (20, 30) mg/day. This could be a reason for the lower effectiveness with DUL seen in our study compared to the previous studies. The pain reduction with PGN in our

Table 2: Mean VAS score difference between baseline and at end of 4, 8, and 12 weeks

Drug	Baseline VAS score (cm)	VAS score difference (cm)		
		4 weeks	8 weeks	12 weeks
AMY (*n*=25)	8.6±1.3	1.1±0.9	1.7±0.9	2.3±1.1
DUL (*n*=25)	7.6±1.4	1.2±1.1	1.3±1.5	1.9±1.3
PGN (*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, AMY: Amitriptyline, DUL: Duloxetine, PGN: Pregabalin

Table 3: Mean difference of VAS scores after adjusting for baseline BMI variability

Drug	Actual mean	Estimated mean[a]	Pairwise comparisons based on estimated marginal means			
			Drugs		Mean difference	Sig.[b]
AMY (*n*=25)	2.32	2.42[a]	AMY	DUL	0.58	0.60
				PGN	−0.22	1.00
DUL (*n*=25)	1.88	1.83[a]	DUL	AMY	−0.58	0.60
				PGN	−0.81	0.17
PGN (*n*=25)	2.68	2.64[a]	PGN	AMY	0.22	1.00
				DUL	0.81	0.17

[a]Covariates appearing in the model are evaluated at the following values: BMI=26.93; [b]Adjustment for multiple comparisons: Bonferroni. VAS: Visual analogue scale, AMY: Amitriptyline, DUL: Duloxetine, PGN: Pregabalin

Table 4: 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	12 weeks	Baseline	12 weeks	Baseline	12 weeks	
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, AMY: Amitriptyline, DUL: Duloxetine, PGN: Pregabalin

Table 5: 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)
Urinary retention (*n* [%])	2 (8)	----	----	2 (2.6)
Dry mouth (*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, AMY: Amitriptyline, DUL: Duloxetine, PGN: Pregabalin

study was 2.68 ± 1.89, that is, ~26%. The previous studies which compared PGN with placebo or active drug showed a reduction in pain severity ranging from 43% to 60%.[19-23] The median dose of PGN used in our study of 75 (75, 112.5) mg/day was much lower than that used in the previous studies which ranged from 150 to 300 mg/day. As our study was an observational study, the dose of drug in each patient was decided by the treating physician. Thus, the doses of all three drugs were those prescribed commonly by clinicians in our population. Moreover, our treating physicians felt that the tolerable dose of these drugs in Indian population is lower than that in the western population. Similarly, dose escalation in individual patients is being done by treating physicians after 3–6 months, which was longer than the follow-up period of our study.

A randomized and controlled trial comparing these three drugs in DPN conducted by Boyle *et al.* showed no significant difference between them in effectiveness, QOL, or safety measures over 28 days of treatment.[25] Although our study showed similar effectiveness of the three drugs, it brought out important difference in QoL parameters that were not seen in the previous study. In our study, PGN was found to be less beneficial in improving total NHP scores than AMY or DUL. When individual domains were analyzed separately, it was found that significant difference was there in improvement of energy, sleep, and emotional reaction. AMY and DUL were better in improving these aspects of QoL compared to PGN. QoL measurements are increasingly recognized as important outcomes in the assessment of chronic diseases. Such information would be useful to enable treatment strategies to be aimed at improving particular aspects of impaired health. Thus, AMY or DUL may be preferred in DPN patients having concomitant features of depression.

All the three drugs were well tolerated and there was no drug discontinuation due to intolerability. Adverse effects with AMY were seen in 20 patients and incidence percentage was 80%. This was comparable to the previous studies which showed an average incidence of adverse effects of 70–80%.[25,26] In the DUL arm, 14 participants had adverse effects with an incidence of 56%. The previous studies also showed an incidence of 60–65% for adverse effects of DUL.[17,18] The PGN arm reported adverse effects in 19 participants and the incidence was 76%. The previous studies also showed similar incidence of adverse effects of 75–80%.[20-23] The similar incidence of adverse effects in our study participants with all three drugs despite lower median doses compared to the previous studies may point to the increased sensitivity to these drugs in our population, providing some credence to the observation of the treating physicians. Sedation and dizziness, the most common adverse effects, were seen in all the three groups. Incidence of sedation was least with PGN treated participants compared to the other two groups. All ADRs were found to be related to the mechanism of action of the drugs and no unexpected or serious ADRs occurred in our study.

The strength of our study was that it was conducted in real-world clinical scenario to assess the effectiveness and safety of the three drugs. However, its limitations included being an observational study of relatively small sample size and short follow-up. Moreover, we have not assessed the effect of change in glycemic status of the participants on the severity of pain in DPN. Other factors contributing to neuropathy such as uremia, vitamin deficiencies, smoking, and hereditary factors were also not assessed in this study.

CONCLUSION

AMY, DUL, and PGN are equally effective and safe as first-line drugs for symptomatic treatment of pain in DPN patients. While PGN had least chance of sedation, it showed lower improvement in QOL than AMY or DUL. Further studies with larger sample size and longer follow-up are required in Indian population to fully assess the effectiveness and safety of drugs for DPN.

REFERENCES

1. Vijayakumar G, Manghat S, Vijayakumar R, Simon L, Scaria LM, Vijayakumar A, *et al*. Incidence of Type 2 diabetes mellitus and prediabetes in Kerala, India: Results from a 10-year prospective cohort. BMC Public Health 2019;19:140.
2. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of Type 2 diabetes: Indian scenario. Indian J Med Res 2012;136:705.
3. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, *et al*. Diabetic neuropathy: A position statement by the American diabetes association. Diabetes Care 2017;40:136-54.
4. Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: Epidemiology, natural history, early diagnosis, and treatment options. Pain Med 2008;9:660-74.
5. Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, *et al*. Prevalence of diabetes and prediabetes in 15 states of India: Results from the ICMR-INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol

2017;5:585-96.
6. Rani PK, Raman R, Rachapalli SR, Pal SS, Kulothungan V, Sharma T. Prevalence and risk factors for severity of diabetic neuropathy in Type 2 diabetes mellitus. Indian J Med Sci 2010;64:51-7.
7. Ashok S, Ramu M, Deepa R, Mohan V. Prevalence of neuropathy in Type 2 diabetic patients attending a diabetes centre in South India. J Assoc Physicians India 2002;50:546-50.
8. Griebeler ML, Morey-Vargas OL, Brito JP, Tsapas A, Wang Z, Leon BG, *et al*. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med 2014;161:639-49.
9. Azmi S, Alam U, Burgess J, Malik RA. State-of-the-art pharmacotherapy for diabetic neuropathy. Expert Opin Pharmacother 2021;22:55-68.
10. Saxena AK, Jain P, Dureja GP, Venkitachalam A, Goswami S, Usmani H, *et al*. Pharmacological management of neuropathic pain in India: A consensus statement from Indian experts. Indian J Pain 2018;32:132-44.
11. Devi P, Madhu K, Ganapathy B, Sarma G, John L, Kulkarni C. Evaluation of efficacy and safety of gabapentin, duloxetine, and pregabalin in patients with painful diabetic peripheral neuropathy. Indian J Pharmacol 2012;44:51-6.
12. Benbow SJ, Wallymahmed ME, MacFarlane IA. Diabetic peripheral neuropathy and quality of life. QJM 1998;91:733-7.
13. Hunt SM, McKenna SP, McEwen J, Backett EM, Williams J, Papp E. A quantitative approach to perceived health status: A validation study. J Epidemiol Community Health 1980;34:281-6.
14. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, *et al*. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 1987;37:589-96.
15. Vrethem M, Boivie J, Arnqvist H, Holmgren H, Lindström T, Thorell LH. A comparison a amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and nondiabetics. Clin J Pain 1997;13:313-23.
16. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250-6.
17. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931-7.
18. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, *et al*. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med 2005;6:346-56.
19. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, *et al*. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67:1411-20.
20. Mittal M, Pasnoor M, Mummaneni RB, Khan S, McVey A, Saperstein D, *et al*. Retrospective chart review of duloxetine and pregabalin in the treatment of painful neuropathy. Int J Neurosci 2011;121:521-7.
21. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: A randomized controlled trial. Neurology 2004;63:2104-10.
22. 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. J Pain 2005;6:253-60.
23. 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.
24. 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;115:254-63.
25. Boyle J, Eriksson ME, Gribble L, Gouni R, Johnsen S, Coppini DV, *et al*. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: Impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care 2012;35:2451-8.
26. Max MB. Endogenous monoamine analgesic systems: Amitriptyline in painful diabetic neuropathy. Anesth Prog 1987;34:123-7.

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