Review Article

Antiepileptic Drugs in Treatment of Pain Caused by Diabetic Neuropathy

Angela M. Gutierrez-Alvarez, MD, MSc, Johnny Beltrán-Rodríguez, MD, and Carlos B. Moreno, MD, EdM
School of Medicine, Universidad del Rosario, Bogotá, Colombia

Abstract
Pain is frequent in diabetic neuropathy and is very hard to manage. Antiepileptic drugs have been used in treating pain for several decades. Their effectiveness has been described in different types of neuropathic pain, but when used as analgesics in painful diabetic neuropathy it still remains controversial. To clarify this effectiveness, a meta-analysis was performed to determine which antiepileptic drug had the best analgesic potential for managing pain in patients suffering from painful diabetic neuropathy. The search covered the Cochrane, MEDLINE, EMBASE, and LILACS databases, between January 1966 and September 2005. The following information was obtained from each article: criteria for diagnosing diabetic neuropathy, patients' age average, antiepileptic drug received and dose, sample size, duration of the disease and treatment follow-up, outcome measurement, evaluation of pain, and rescue medication. A combined 2.33 relative risk (95% confidence interval [CI] 1.88–2.88) was obtained; this result indicated that the antiepileptic drugs studied were effective for controlling pain in diabetic neuropathy. The corresponding necessary number to treat (NNT) values were established for evaluating which antiepileptic drug was most effective as an analgesic, according to our interests; pregabalin was shown to be the antiepileptic drug having the lowest NNT (NNT = 3.24 and 95% CI 2.12–6.81) for achieving greater than 50% analgesia in patients suffering from painful diabetic neuropathy. Antiepileptic drugs are frequently used in the specific case of diabetic neuropathy; the combined result of this meta-analysis has demonstrated their analgesic benefit. J Pain Symptom Manage 2007;34:201–208.

Key Words
Diabetic neuropathies, pain, anticonvulsants, neuropathy, treatment, meta-analysis, randomized controlled trials

Introduction

Pain is one of diabetic neuropathy's most common and incapacitating symptoms; its pharmacological control is difficult. Pain treatment thus represents one of the greatest challenges in the clinical management of this disease.[1,2]

Neuropathy is one of the most frequent complications of diabetes.[3] Its incidence

There is no actual or potential financial or other conflict of interest related to the manuscript.

Address reprint requests to: Angela M. Gutierrez-Alvarez, MD, Universidad del Rosario, Research Office, School of Medicine, Calle 63D No. 24–31, Bogotá, Colombia. E-mail: amgutier@urosario.edu.co

Accepted for publication: October 20, 2006.

0885-3924/07/$–see front matter
doi:10.1016/j.jpainsymman.2006.10.023

increases with the duration of the disease, and over time, as many as 50% of patients can be affected.[4,5] It is a heterogeneous disorder that may affect sensory, motor, and autonomic nerves.[3,6] The commonest type is a symmetric distal sensorimotor polyneuropathy, in which pain is a predominant symptom.[7]

Antiepileptic drugs have been used in treating pain for several decades. Their effectiveness has been described in different types of neuropathic pain,[8–11] but their effectiveness when used as analgesics in painful diabetic neuropathy remains controversial. Given the appearance of new antiepileptic drugs on the market, systematic and rigorous evaluation of their effectiveness in managing painful diabetic neuropathy has become necessary when making evidence-based clinical recommendations. To clarify the evidence, a meta-analysis was performed to determine which antiepileptic drugs have the best analgesic potential for managing pain in patients suffering from painful diabetic neuropathy.

Materials and Methods

A search was carried out and systematic selection was made of all clinical trials for analgesic treatment of diabetic neuropathy with antiepileptic drugs that had been published between January 1966 and September 2005. The search covered the Cochrane, MEDLINE, EMBASE, and LILACS databases, using combinations of the following MeSH terms: "diabetic neuropathies," "pain," "anticonvulsants," "therapy (subheading)," "treatment outcome," "therapies, investigational," "neuropathy," and "treatment." The only search limits imposed were human clinical trials and publications in English or Spanish. The search was done electronically; the titles and content of the summaries of corresponding articles were analyzed and the complete text was obtained of those considered to be pertinent. All references presented in each article were reviewed. The following journals were manually consulted for identifying other relevant articles: Acta Neurologica Scandinavica, Archives of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Neurology, New England Journal of Medicine, Pain, Revista de Neurología, and The Lancet. Those randomized clinical trials (RCTs) comparing a product with a placebo were included if they studied the analgesic effect of antiepileptic drugs in adults suffering from painful diabetic neuropathy (i.e., evaluated in such a way that improvement could be objectively measured). Excluded studies included those that contained no relevant categorical measurements, case reports, summarized publications, and studies of treatments still in the research phase. All studies were independently read by all three current authors and the validity of each trial to be included was based on five parameters: method of assigning participants to an intervention within the study, blinding, follow-up, definitions regarding cases, and clinical results. Jadad et al.'s guidelines[12] also were followed, and an assessment performed (Table 1).

The following information was obtained from each article: criteria for diagnosing diabetic neuropathy, patients' age average, antiepileptic drug received and dose, sample size, duration of the disease and treatment follow-up, outcome measurement, evaluation of pain, and rescue medication. Any discrepancy was resolved by consensus.

Statistical Analysis

The data were set out in contingency tables in which the rows showed exposure to antiepileptic drug and the columns improvement regarding pain; the response variable was

Table 1
Assessment Using Jadad et al.'s Guidelines[a]

Study	Year	Jadad et al.'s Score
1. Rull—carbamazepine[13]	1969	3
2. Chadda—phenytoin[14]	1978	2
3. Backonja—gabapentin[15]	1998	5
4. Gorson—gabapentin[16]	1999	2
5. Eisenberg—lamotrigine[17]	2001	5
6. Kochar—valproic acid[18]	2002	3
7. Lesser—pregabalin 600[19]	2004	5
8. Lesser—pregabalin 300[19]	2004	5
9. Otto—valproic acid[20]	2004	5
10. Raskin—topiramate[21]	2004	5
11. Rosenstock—pregabalin[22]	2004	5
12. Dogra—oxcarbazepine[23]	2005	5
13. Freynhagen—pregabalin[24]	2005	3
14. Freynhagen—pregabalin[24]	2005	3
15. Richter—pregabalin[25]	2005	5

[a]Jadad et al.'s scale to judge the quality of trials is based on the following parameters: randomization, blinding, and withdrawals description (maximum 5; minimum 1).

binary. Measurement of effect was defined as relative risk (RR). The following tests were performed: 1) DerSimonian and Laird's test and Galbraith's plot for establishing heterogenicity; 2) individual and combined results table for fixed and random effects model, and meta-analysis and accumulated meta-analysis plots for combining results; and 3) funnel plot and Begg and Egger's tests for publication bias. Pan-American Health Organization Epidat software (version 3.0, December 2003) was used for the meta-analysis (a program for epidemiological analysis of tabulated data). Necessary number to treat (NNT) values were calculated for each antiepileptic drug, as well as NNT 95% confidence interval (CI) based on the following formulae: NNT = 1/ARR and 95% CI NNT = reciprocal of ARR 95% CI.

$$\text{ARR 95\% CI} = \text{ARR} \pm 1.96\,\text{SE}_{\text{ARR}}$$

where ARR = absolute risk reduction.

Results

This research included 2035 adult patients from 15 RCTs[13–25] published between 1969 and 2005. The analgesic effects of the following antiepileptic drugs were investigated: carbamazepine, phenytoin, gabapentin, lamotrigine, valproic acid, pregabalin, topiramate, and oxcarbazepine (Table 2). Patients had been randomly assigned to the intervention group or control group in all studies. The variable used was some degree of improvement of pain (as measured by an objective test) and RR as measurement of effect.

Four studies[26–29] were excluded from the analysis because they did not provide sufficient categorical data for drawing up contingency tables. Another three studies[30–32] did not fulfill all the selection criteria. The Q test proposed by DerSimonian and Laird[33] was used for evaluating the degree of heterogenicity and determining whether the results from different studies could be summarized in just one measurement; this indicated a 95% confidence level and statistical evidence of heterogenicity ($P = 0.0001$, Chi-square = 41.73 with 14 df). A clear influence of studies by Rull et al.,[13] Otto et al.,[20] and Rosenstock et al.[22] was noted as they have contributed most toward heterogenicity; values were seen to be outside Galbraith's plot confidence bands (Fig. 1).

Given the heterogenicity obtained, subgroup analysis was undertaken, which included 1129 patients from 6 RCTs carried out between 2004 and 2005, which evaluated the change to oxcarbazepine, pregabalin, or topiramate. All these studies explicitly reported the number of patients improved by more than 50% in terms of perception of pain, respecting the baseline, and evaluated improvement of pain using very similar parameters. The results obtained when analyzing the subgroup are shown in Table 3 and Fig. 2. Freynhagen et al.'s study[24] was excluded (in spite of being methodologically similar to the other subgroup analysis studies), as it did not allow data corresponding to patients suffering from neuropathy who had antecedents of diabetes to be identified.

Table 2
Meta-Analysis of 15 RCTs Analyzing Any Degree of Analgesia from Different Anticonvulsants in Diabetic Neuropathy

Study	Year	*n*	RR	95% CI
1. Rull—carbamazepine[13]	1969	60	1.12	0.93, 1.35
2. Chadda—phenytoin[14]	1978	76	2.80	1.59, 4.93
3. Backonja—gabapentin[15]	1998	162	1.84	1.28, 2.64
4. Gorson—gabapentin[16]	1999	40	2.09	1.24, 3.50
5. Eisenberg—lamotrigine[17]	2001	53	2.12	1.26, 3.55
6. Kochar—valproic acid[18]	2002	52	3.43	1.52, 7.74
7. Lesser—pregabalin 600[19]	2004	177	1.96	1.42, 2.71
8. Lesser—pregabalin 300[19]	2004	177	1.85	1.33, 2.58
9. Otto—valproic acid[20]	2004	62	0.37	0.11, 1.28
10. Raskin—topiramate[21]	2004	317	1.46	1.08, 1.96
11. Rosenstock—pregabalin[22]	2004	146	4.60	2.04, 10.39
12. Dogra—oxcarbazepine[23]	2005	146	1.57	1.01, 2.44
13. Freynhagen—pregabalin[24]	2005	197	1.80	1.28, 2.54
14. Freynhagen—pregabalin[24]	2005	206	1.59	1.13, 2.25
15. Richter—pregabalin[25]	2005	164	2.67	1.48, 4.80

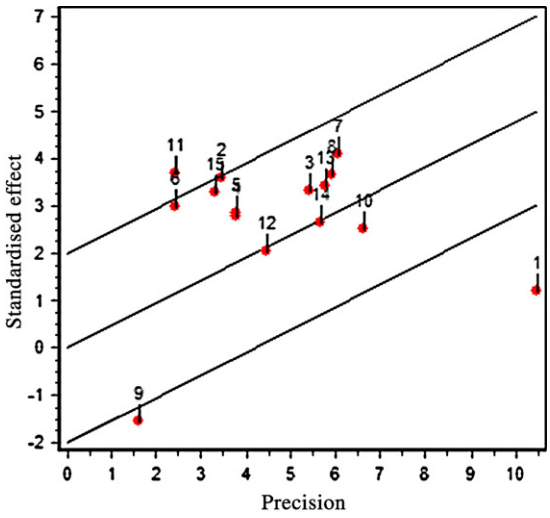

Fig. 1. Galbraith's plot for determining the degree of heterogenicity, where: 1. Rull—carbamazepine, 2. Chadda—phenytoin, 3. Backonja—gabapentin, 4. Gorson—gabapentin, 5. Eisenberg—lamotrigine, 6. Kochar—valproic acid, 7. Lesser—pregabalin 600, 8. Lesser—pregabalin 300, 9. Otto—valproic acid, 10. Raskin—topiramate, 11. Rosenstock—pregabalin, 12. Dogra—oxcarbazepine, 13. Freynhagen—pregabalin, 14. Freynhagen—pregabalin, and 15. Richter—pregabalin. The Rull et al.,[13] Otto et al.,[20] and Rosenstock et al.[22] studies have contributed toward heterogenicity, because values were outside Galbraith's plot confidence bands.

DerSimonian and Laird's heterogenicity test for the subgroup consisting of the six selected RCTs indicated 95% confidence level; however, there was no evidence of statistical heterogenicity ($P = 0.28$, Chi-square = 6.42 with 5 df). This result agreed with that observed in the Galbraith plot (Fig. 3).

A funnel plot was used for discarding publication bias (Fig. 4) and for contrasting the null hypothesis regarding the absence of Begg[34]

Table 3
Analysis of the Subgroup of Six RCTs Analyzing the Analgesic Effect (>50% with Regard to Baseline) of Different Anticonvulsants in Diabetic Neuropathy

Study	Year	*n*	RR	95% CI
Lesser—pregabalin 600	2004	178	2.75	1.69, 4.47
Lesser—pregabalin 300	2004	178	2.61	1.59, 4.27
Raskin—topiramate	2004	317	1.69	1.12, 2.53
Rosenstock—pregabalin	2004	146	4.60	2.04, 10.39
Dogra—oxcarbazepine	2005	146	1.91	1.09, 3.39
Richter—pregabalin	2005	164	2.67	1.48, 4.80
Fixed effects		1129	2.33	1.88, 2.89
Random effects		1129	2.37	1.85, 3.04

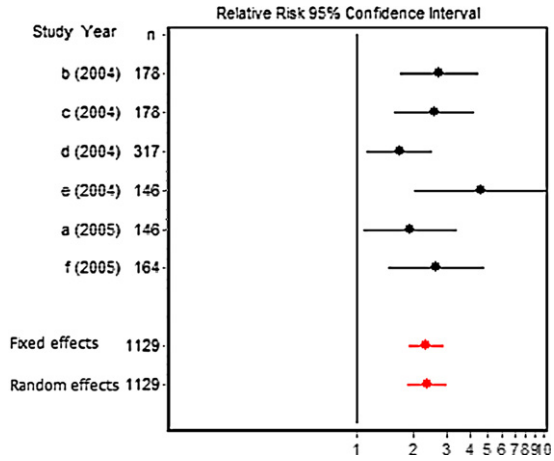

Fig. 2. RCT subgroup forest plot, where b = lesser-pregabalin 600, c = lesser-pregabalin 300, d = Raskin-topiramate, e = Rosenstock-pregabalin, a = Dogra-oxcarbazepine, f = Richter-pregabalin.

($P = 0.45$, $Z = 0.75$) and Egger test[35] ($P = 0.09$, $t = 2.18$ with 4 df) publication bias. NNTs were calculated with their respective CIs for antiepileptic drugs included in the definitive meta-analysis (Fig. 5).

Discussion

Pain is frequent in diabetic neuropathy and is very hard to manage. Tricyclic antidepressants[31,36,37] have generally been proposed for

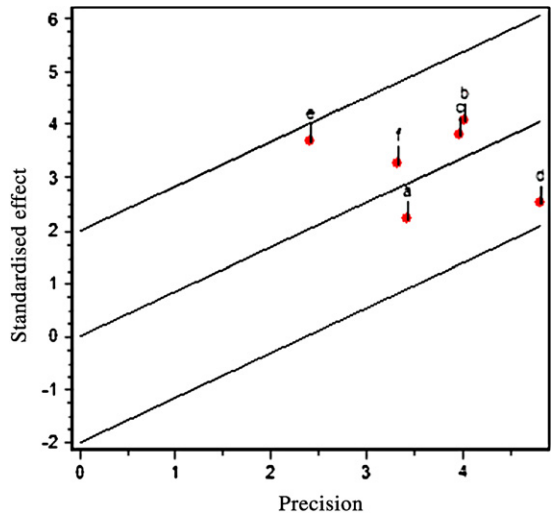

Fig. 3. Galbraith's plot for determining the degree of heterogenicity when analyzing the subgroup of six RCTs. There was no evidence of statistical heterogenicity, because there were no studies outside Galbraith's plot confidence bands.

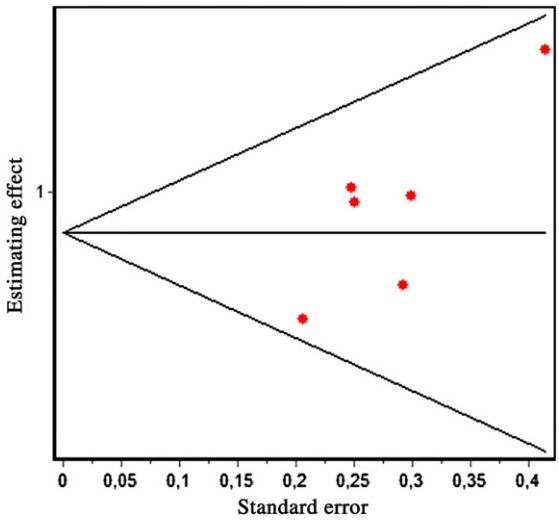

Fig. 4. Funnel plot for discarding publication bias for the selected RCTs in subgroup analysis. Although this statistical test suggests that there was no publication bias in this group of studies (all the studies are included in the funnel plot), it is known that several antiepileptic drugs have been tested in this condition without the results ever being published.

treating neuropathic pain as first-line medications and antiepileptic drugs have been considered to be second-line medications due to their ability to suppress neuronal hyperexcitability.[38] Even though managing pain is ideally achieved by improving patients' condition with just one medication, around 30% of patients suffering from neuropathic pain do not respond suitably to monotherapy. Combined therapy[38] must, therefore, be provided in such cases. Antiepileptic drugs are frequently used in the specific case of diabetic neuropathy; the combined result of this meta-analysis has demonstrated their analgesic benefit. Hyperglycemia treatment is also required in these patients in addition to analgesic medication. Poorly controlled levels of glycemia contribute toward worsening neuropathy and hamper managing pain.[39]

Two different meta-analyses were performed for interpreting the results of this study. The first one included all studies fulfilling the selection criteria (Table 2). It was found that the studies were very heterogeneous in both clinical and statistical aspects, as the follow-up periods were different and the outcome of most work did not establish the magnitude of analgesia considered to be clinically significant. The studies could not be compared to one another and the conclusions were only applicable to each separate study, thereby limiting the clinical application of this combined analysis. The foregoing led to carrying out a second meta-analysis (subgroup analysis, Table 3) using those studies which specifically reported 50% or greater improvement of pain as the criteria for considering the clinical effectiveness of a particular antiepileptic drug used. These were also studies having similar methodology and a minimum of 5 weeks follow-up. Statistical homogeneity was shown in this group of studies. Although statistical tests suggest that there was no publication bias in this group of studies (Fig. 4), it is known that several antiepileptic drugs have been tested in this condition without the results ever being published. In fact, some of these studies have been presented as congress abstracts,[40–43] showing that a specific antiepileptic drug (topiramate) may be useful in the treatment of diabetic neuropathic pain. Caution should be taken against interpreting the results exclusively on the basis of published data.

A combined 2.33 RR (95% CI 1.88–2.89) was obtained; this result indicated that the three antiepileptic drugs studied were effective for controlling pain in diabetic neuropathy. Even though the number of studies may have been small (6 studies), all presented positive results, had been published recently, and included 1129 patients from the 2035 involved in the initial analysis (55% of cases). The corresponding NNTs (Fig. 5) were established for evaluating which antiepileptic drug was most effective as an analgesic, according to our interests; pregabalin was shown to be the antiepileptic drug having the lowest NNT (NNT = 3.24 and 95% CI 2.12–6.81) for achieving greater than 50% analgesia in patients suffering from painful diabetic neuropathy. Nevertheless, there are few differences between the studied drugs. Accordingly, to select the final analgesic treatment, the side effects of all these drugs must be considered. The most common side effects are somnolence or drowsiness, nausea or vomiting, and dizziness.

Meta-analysis concerning the analgesic effect of antiepileptic drugs in patients suffering from diabetic neuropathy had two limitations. The first was the lack of consensus in classifying diabetic neuropathy,[1] hampering comparing the groups being investigated. The second lay in the difficulty in precisely and objectively evaluating pain; even though the

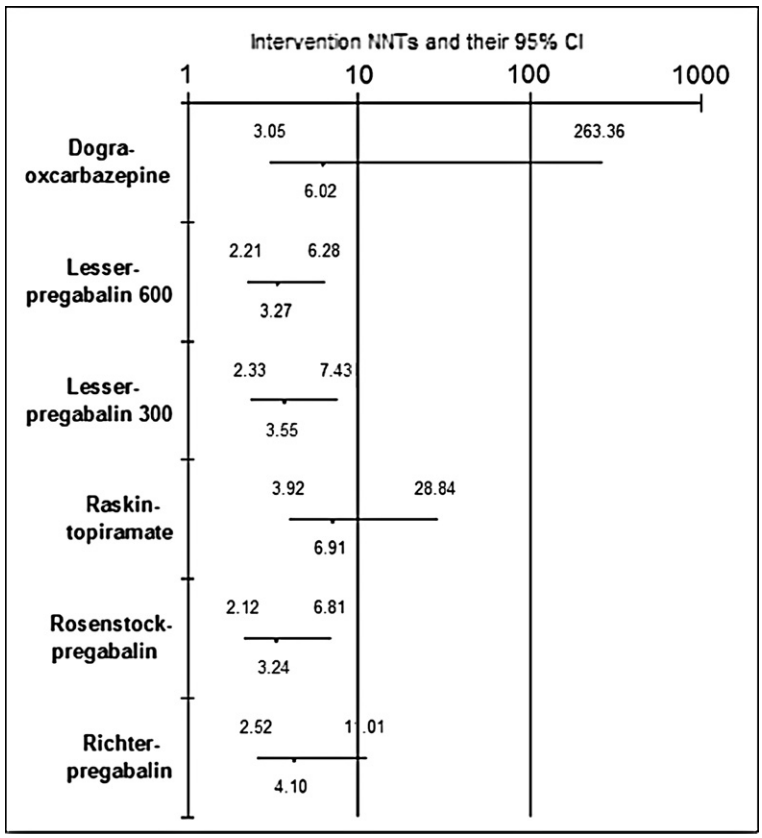

Fig. 5. NNTs for studies reporting greater than 50% reduction of pain with regard to baseline. NNT is the number of patients that need to be treated to get 50% reduction of pain in one of them.

visual analog scale is generally used for evaluating its intensity, there is still discussion about the clinical interpretation of this scale[44] and other similar ones. These instruments can also lose their reliability when the intensity of a particular pain is not evaluated at the same time as it is being felt, because memory is unreliable regarding pain. On the other hand, pain involves other dimensions, such as duration, quality, and localization, which cannot be quantified using these scales.

Future studies concerning this topic should consider administering the medication over more prolonged periods of time and objectively evaluating their effects on quality of life in dimensions such as sleep, effects on work, social life, and state of mind.

References

1. Sinnreich M, Taylor BV, Dyck PJB. Diabetic neuropathies. Classification, clinical features and pathophysiological basis. Neurologist 2005;11(2):63–79.

2. Vinik AI. Diabetic neuropathy: pathogenesis and therapy. Am J Med 1999;107(2B):17S–26S.

3. Kelkar P. Diabetic neuropathy. Semin Neurol 2005;25(2):168–173.

4. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care 2003; 26(6):1790–1795.

5. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 2002;18(6): 350–354.

6. Polydefkis M, Griffin JW, McArthur J. New insights into diabetic polyneuropathy. JAMA 2003; 290:1371–1376.

7. Greene DA, Stevens MJ, Feldeman EL. Diabetic neuropathy: scope of the syndrome. Am J Med 1999;107(2B):2S–8S.

8. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs form the management of pain: a systematic review. BMJ 1995;311: 1047–1052.

9. McQuay HJ, Moore RA, Eccleston C, Morley S, Williams AC. Systematic review of outpatient

services for chronic pain control. Health Technol Assess 1997;1(6):i–iv. 1–135.

10. Wiffen P, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. Cochrane Database Syst Rev 2000;2: CD001133.

11. Wiffen P, Collins S, McQuay H, et al. Anticonvulsant drugs for acute and chronic pain. Cochrane Database Syst Rev 2000;3:CD001133.

12. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17: 1–12.

13. Rull JA, Quibrera R, González-Millán H, Lozano Castañeda O. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (tegretol): double blind crossover trial. Diabetologia 1969;5: 215–218.

14. Chadda VS, Mathur MS. Double blind study of the effects of diphenylhydantoin sodium on diabetic neuropathy. J Assoc Physicians India 1978;26: 403–406.

15. Backonja M, Beydoun A, Edwards K, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. JAMA 1998;280(21):1831–1836.

16. Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry 1999;66(2):251–252.

17. Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy. Neurology 2001;57:505–509.

18. Kochar DK, Jain N, Agrawal RP, et al. Sodium valproate in the management of painful neuropathy in type 2 diabetes—a randomized placebo controlled study. Acta Neurol Scand 2002;106(5): 248–252.

19. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004;63:2104–2110.

20. Otto M, Bach FW, Jensen TS, Sindrup SH. Valproic acid has no effect on pain in polyneuropathy: a randomized controlled trial. Neurology 2004;62: 285–288.

21. Raskin P, Donofrio PD, Rosenthal NR, et al. Topiramate vs. placebo in painful diabetic neuropathy: analgesic and metabolic effects. Neurology 2004;63:865–873.

22. 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;110:628–638.

23. Dogra S, Beydoun S, Mazzola J, Hopwood M, Wan Y. Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. Eur J Pain 2005;9(5):543–554.

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: 254–263.

25. Richter RW, Portenoy R, Scharma U, et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized placebo-controlled trial. J Pain 2005;6:253–260.

26. Wilton TD. Tegretol in the treatment of diabetic neuropathy. S Afr Med J 1974;48(20):869–872.

27. Thienel U, Neto W, Schwabe SK, Vijapurkar U. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol Scand 2004;110:221–231.

28. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352:1324–1334.

29. Saudek CD, Werns S, Reidenberg MM. Phenytoin in the treatment of diabetic symmetrical polyneuropathy. Clin Pharmacol Ther 1977;22(2): 196–199.

30. Beydoun A, Kobetz SA, Carrazana EJ. Efficacy of oxcarbazepine in the treatment of painful diabetic neuropathy. Clin J Pain 2004;20:174–178.

31. Sindrup S, Jensen T. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999;83:389–400.

32. Duby JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. Diabetic neuropathy: an intensive review. Am J Health Syst Pharm 2004;61(2): 160–176.

33. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.

34. Begg CB, Mazumbar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101.

35. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.

36. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003;60(11):1524–1534.

37. Sindrup S, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. Neurology 2000;55: 915–920.

38. Namaka M, Gramlich CR, Ruhlen D, et al. A treatment algorithm for neuropathic pain. Clin Ther 2004;26(7):951–979.

39. Nathan DM. The pathophysiology of diabetic complications: how much does the glucose hypothesis explain? Ann Intern Med 1996;124:86–89.

40. Edwards K, Glantz M, Button J, Norton J, Whittaker T. The evaluation of topiramate in the management of painful diabetic neuropathy. Poster #703, presented at the 18th Annual Meeting of the American Pain Society, 1999.

41. Rosenthal N, Hewitt D, Jordan D, Xiang J, Hulihan J. Topiramate in the treatment of painful diabetic neuropathy: results from a multicenter randomized double blind placebo controlled trial. Presented at the 5th International Conference on the mechanisms and treatment of neuropathic pain, Bermuda, 2002.

42. Rosenthal N, Hewitt D, Jordan D, Xiang J. Topiramate in the treatment of painful diabetic neuropathy: results from a multicenter randomized double blind placebo controlled trial. Poster #9477, presented at the 22nd Annual Meeting of the American Pain Society, Chicago, Illinois, 2003.

43. Vinik A, Roanoke VA, Hewitt D, et al. Topiramate in the treatment of painful diabetic neuropathy: results from a multicenter randomized double blind placebo controlled trial. Poster #2.149, presented at the 55th Annual Meeting of the American Academy of Neurology, Honolulu, Hawaii, 2003.

44. Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? Pain 2003;105: 151–157.