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# Treatment of intractable painful diabetic neuropathy with intravenous lignocaine

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**Abstract**

**Objective:** Lignocaine is a cardiac antiarrhythmic agent occasionally used to treat neuropathic pain. This study was designed to examine the effectiveness of intravenous lignocaine in patients with intractable painful diabetic neuropathy. **Research design and methods:** Fifteen patients with painful diabetic peripheral neuropathy, who had appeared to respond to previous lignocaine infusions, completed a double-blind, placebo-controlled crossover trial of two doses of intravenous lignocaine (5 and 7.5 mg/kg) versus saline. Infusions were administered in random order over 4 h at four weekly intervals. The effect of treatment on pain perception was assessed using the McGill Pain Questionnaire (MPQ), a daily pain diary, hours of sleep, fasting blood glucose, and use of other pain-relieving medication. **Results:** Both doses of lignocaine significantly ($P<.05$ to $P<.001$ for the different measures) reduced the severity of pain compared with placebo. This reduction was present at both 14 and 28 days after the infusion. The qualitative nature of the pain was also significantly ($P<.05$ to $P<.01$) modified by lignocaine compared with placebo for up to 28 days. The preceding dose 4 weeks earlier significantly ($P<.01$ and $P<.001$) affected the response to the next dose. There were no significant effects of treatment on the other measures of response. There were no significant side effects of the treatment. **Conclusions:** This study shows that intravenous lignocaine ameliorates pain in some diabetic participants with intractable neuropathic pain who have failed to respond to or are intolerant of available conventional therapy.


*Keywords:* Diabetes mellitus; Intractable painful neuropathy; Lignocaine infusion; McGill Pain Questionnaire

## 1. Introduction

Peripheral neuropathy is a common complication of Types 1 and 2 diabetes (Dyck, Kratz, & Karnes, 1993; Young, Boulton, McLeod, Williams, & Sonksen, 1993). While it is often asymptomatic, it may be painful and debilitating (Galer, Gianas, & Jensen, 2000; Veves, Manes, Murray, Young, & Boulton, 1998) and, in many cases, difficult to manage.

Good glycaemic control reduces the prevalence of peripheral neuropathy in patients with diabetes (Diabetes Control and Complications Trial Research Group, 1995; UK Prospective Diabetes Study Group, 1998). Results of prevention studies with other metabolic interventions (aldose reductase inhibitors, neurotrophins, and antioxidants; Bril, 2001) have been generally disappointing.

Placebo controlled trials of treatments for painful diabetic peripheral neuropathy have confirmed some efficacy in reducing pain for tricyclic antidepressants (McQuay et al., 1996), anticonvulsants (Backonja et al., 1998; Eisenburg, Lurie, Braker, Daoud, & Ishay, 2001; Iacobellis, Allen, & Lamoreaux, 2000; McQuay, Carroll, Jadad, Wiffen, & Moore, 1995), nonsteroidal anti-inflammatory drugs (NSAIDs; Cohen & Harris, 1987), and more recently,

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isosorbide dinitrate spray (Yuen, 2002). Most of the trials indicate about a 30% response rate. Consequently, neuropathic pain is commonly treated empirically with tricyclic antidepressants, anticonvulsant drugs, and NSAIDs, either individually or in combination, and in severe cases, with opioids.

Intravenous lignocaine (Winters, Kast, Simpson, & Newnham, 1996) and oral mexiletine (Dejgard, Peterson, & Kastrup, 1988; Oskarsson, Lins, Ljunggren, & Mexiletine study group, 1992; both cardiac antiarrhythmic drugs) have been reported to be of benefit in reducing neuropathic pain. Although one controlled trial (Kastrup, Peterson, Dejard, Angelo, & Hilstead, 1987) with intravenous lignocaine has been published and short duration benefit reported, this mode of therapy has not been commonly adopted, nor has its place in the range of available therapies been evaluated.

We have observed apparent benefit from intravenous lignocaine in many patients with intractable painful diabetic peripheral neuropathy. In this double-blinded, placebo-controlled crossover study, we have examined the effect of lignocaine in a group of "apparent lignocaine responders." The study was designed to see whether the response was due to the supportive environment of the infusion or a genuine effect of the drug.

Table 1
Patients' demographics and baseline characteristics

| Characteristic | *N*=15 |
|---|---|
| Gender | |
| Male/Female | 7/8 |
| Age (mean±S.D.) [years] | 64.3 ± 13.3 |
| Duration (mean±S.D.) [years] | |
| Diabetes | 18.8 ± 9.7 |
| Neuropathic pain | 5.1 ± 3.3 |
| Hypoglycaemic treatment | |
| Insulin/oral agents | 12/4 |
| Neurological/sensory details | |
| Distribution of neuropathic pain | |
| Foot/toes | 15 |
| Leg | 6 |
| Hand/finger | 3 |
| Arm | – |
| Decreased/absent ankle reflexes | 13 |
| Decreased/absent pinprick sensation | |
| Hand/arm | 8 |
| Foot | 13 |
| Leg | 12 |
| Decreased/absent vibration sensation | |
| Hand | 5 |
| Foot | 15 |

## 2. Research design and methods

### 2.1. Participants

Following an apparent dramatic response to lignocaine (5 mg/kg body weight; Kastrup et al., 1987) in a woman with intractable neuropathic pain in 1993, we established the lignocaine infusion program for participants with Types 1 and 2 diabetes suffering from painful neuropathy. The patients were either inadequately responsive to or were intolerant of conventional therapy (NSAIDs, tricyclic antidepressants, and anticonvulsants drugs). Fifty-three patients have received initial treatment in the program, with 27 patients continuing in the program after responding to the initial infusion and receiving at least four infusions at approximately four weekly intervals. Twenty-two of these patients with stable diabetes management and neuropathic symptoms for at least 12 months were invited to participate in this study. Seventeen patients provided informed written consent; two subsequently withdrew consent prior to commencing the trial for reasons unrelated to the study.

The characteristics of the 15 patients completing the study are summarized in Table 1. Painful diabetic neuropathy is a clinical diagnosis based on symmetrical symptoms of burning, stabbing, tightness, numbness, and/or aching pain distally in the lower limbs with a consistent exacerbation at night or during periods of rest and signs of a peripheral neuropathy.

This was an outpatient, randomised, double-blinded, and placebo-controlled crossover study. Prior to commencing the study, all participants were in an established treatment program receiving lignocaine infusions (5 mg/kg) at four weekly intervals. For ethical reasons, there was no prolonged washout or withdrawal of therapy prior to undertaking the study.

Throughout the study, patients were permitted to take their usual treatments, principally NSAIDs, used for pain relief. No patients were taking tricyclic antidepressants or anticonvulsants during the trial, as all of these drugs had previously been reported as ineffective.

### 2.2. Lignocaine infusion

Identical 500 ml normal saline flasks were prepared by the hospital pharmacy with lignocaine concentrations of 0 mg/500 ml (placebo, P), 500 mg/500 ml (L), and 750 mg/500 ml (H). The participants received the three study doses at four weekly intervals in random order (randomisation performed by the hospital pharmacy department). The three sequences (of a possible nine) chosen were P–L–H, L–H–P, and H–P–L, and all sequences were used five times. Lignocaine is an odourless and colourless solution, and infusions were performed through a peripheral vein over 4 h and administered to a total dose of 5 ml/kg. All participants were under constant observation with regular blood pressure monitoring during the infusions for signs or symptoms of possible reactions to lignocaine. For the first 7 years of the program, patients were also on telemetry to monitor for cardiac arrhythmias during the infusion. As there were no events recorded during this time, it was deemed unnecessary to continue with telemetry monitoring during the study.

### 2.3. Measures of outcome

The primary efficacy measure for pain was the widely used and validated long form McGill Pain Questionnaire (MPQ; Melzack, 1975). The MPQ is designed to provide quantitative measures of clinical pain that can be treated statistically. Three types of pain data obtained from the MPQ are:

(a) The number of words chosen (NWC) relates to the number of descriptors respondents used to describe their pain.
(b) The present pain intensity (PPI) is based on a single choice of a numbered word.
(c) The pain rating index based on the rank value of the words (PRI(R)) enables respondents to report changes in pain intensity while still acknowledging the presence of different dimensions of pain.

The MPQ also divides pain into three categories; sensory, affective, and evaluative. Sensory pain descriptors, such as shooting, pricking, sharp, burning, and tingling, are contained in the first 10 items. Affective descriptors such as tiresome, exhausting, sickening, and cruel are in the next 4, while the evaluative descriptors, troublesome, annoying, intense, or unbearable, are assessed by a single item.

Secondary efficacy measures were the following:

(a) Patient journals recording daily pain evaluation on a scale from 0 (*none*) to 5 (*excruciating*).
(b) Daily recording of hours of sleep, fasting blood glucose, other pain-relieving medications used, and unusual or adverse events.

Prior to the commencement of each infusion, participants completed an MPQ questionnaire, and daily recording journals were issued. At the midpoint (Day 14 between treatments), participants again completed an MPQ questionnaire at home and brought the forms to their next appointment.

The end of the study for all patients was 28 days after the third infusion when the final home recording charts and the midpoint MPQ evaluations were collected. The safety of lignocaine was assessed from adverse events recorded during each infusion and from the daily recording journal.

### 2.4. Statistical analysis

The MPQ data for each treatment was compared by analysis of variance (ANOVA) and Tukey's post hoc test. The effect of the preceding dose on the response to a subsequent treatment was assessed by analysis of covariance (ANCOVA). This analysis was required, as no prolonged period of washout was allowed after the previous dose. The current dose and change in dose from the preceding 4 weeks were treated as quantitative variables. The effect of treatment on hours of sleep, other medication usage (number of tablets taken each month), home assessment of pain, and the fasting blood glucose levels was assessed using the ANOVA.

This study complies with the Helsinki declaration, and the protocol was viewed and approved by the hospital ethics committee prior to commencing the study.

## 3. Results

While all 15 participants completed all the MPQ questionnaires, there were three partially or totally incom-

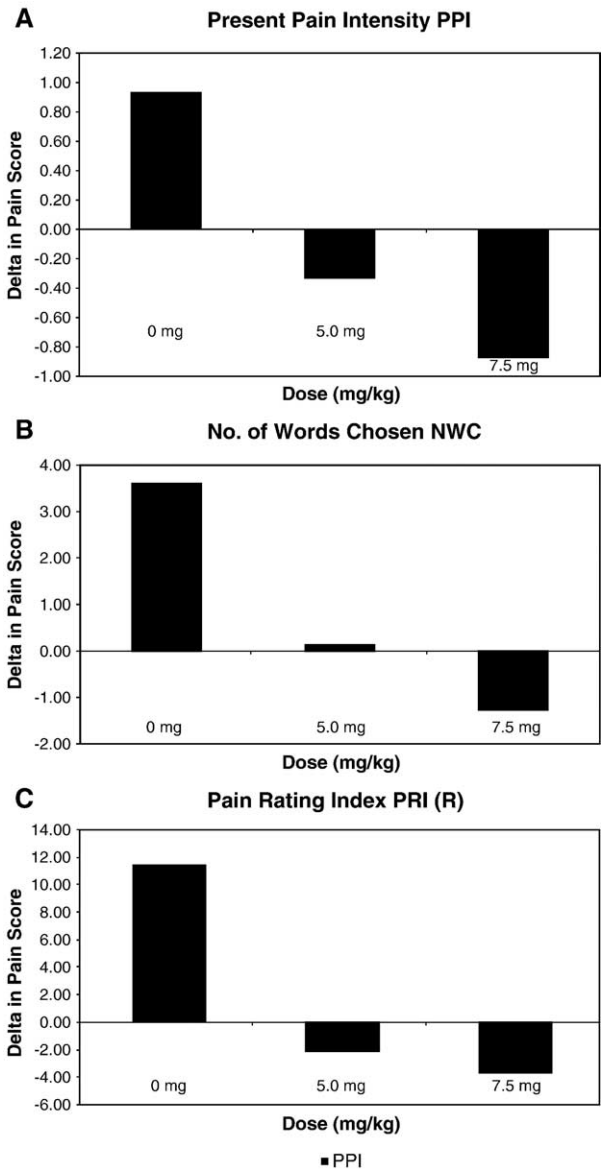


Fig. 1. (A) The difference in PPI between 0 and 14 days for placebo and 5.0 and 7.5 mg/kg lignocaine. $P < .01$ for each dose against placebo. (B) The difference in NWC between 0 and 14 days for placebo and 5.0 and 7.5 mg/kg lignocaine. $P < .05$ for each dose against placebo. (C) The difference in PRI(R) between 0 and 14 days for placebo and 5.0 and 7.5 mg/kg lignocaine. $P < .01$ for each dose against placebo.

plete daily recording journals. Data for these three patients were excluded from the analysis of daily journal information.

The differences between the changes in MPQ data between 0 and 14 days for all three treatments were significant (NWC, $P<.05$; PRI(R), $P<.01$; PPI, $P<.001$; ANOVA). The differences between placebo and 5 and 7.5 mg/kg of lignocaine are shown in Fig. 1A–C. The placebo arm of the study followed active treatment with either dose of lignocaine. The mean change in pain score for PRI(R) and PPI was significant for both 5 and 7.5 mg/kg lignocaine compared with placebo ($P<.05$ for both, Tukey's post hoc test). The mean change for NWC of 7.5 mg/kg, but not 5 mg/kg, lignocaine compared with placebo was significant (Tukey's post hoc test). There was no significant difference between the MPQ scores (PRI(R), PPI, and NWC) for each treatment between Days 14 and 28. While there was a trend to a greater response for 7.5 mg/kg lignocaine compared with 5 mg/kg, this did not reach significance for any of the scores.

When examining the influence of the treatment in the previous 4 weeks, the change in dose (here treated as a quantitative variable) is seen to strongly influence the pain scores (NWC, $P<.01$; PRI(R), $P<.001$; PPI, $P<.001$; ANCOVA).

Analyses of the three categories of pain, sensory, affective, and evaluative, were also analysed by ANOVA and Tukey's post hoc test. Sensory pains were significantly improved by lignocaine at both 5 and 7.5 mg/kg dosages ($P<.01$; Fig. 2). Affective and evaluative pains were significant ($P<.05$) at the 7.5 mg/kg dose alone. The differences were again significant by 14 days and remained unchanged at 28 days.

There was no significant difference between the three treatments for the number of pain-relieving medications used during the 4 weeks (ANOVA). There was also no significant difference in the mean fasting blood glucose levels, the mean hours of sleep, and the mean daily pain scores recorded in the daily journal (ANOVA) between the three treatments (data not provided).

Throughout the infusions and during the weeks between infusions, there was only one reported adverse side effect in one patient (light-headedness during infusion with 7.5 mg/kg lignocaine).

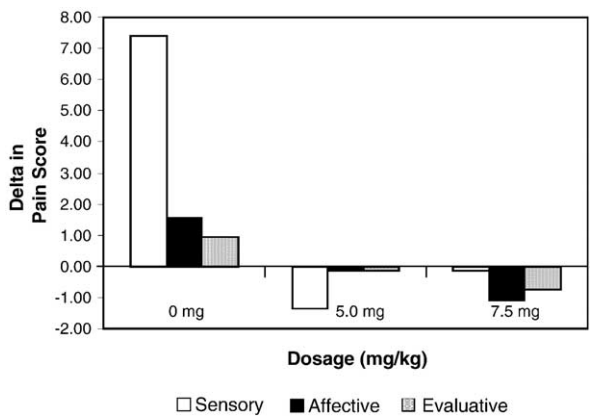


Fig. 2. Comparison of pain qualities. Details for pain scores between 0 and 14 days according to the three main categories: sensory(white), affective (black), and evaluative (hatched). $P<.01$ for sensory pain for 5 and 7.5 mg/kg compared with the placebo. $P<.05$ for both affective and evaluative pain at 7.5 mg/kg compared with the placebo.

## 4. Conclusions

Painful diabetic neuropathy can be a challenging condition to manage. Controlled trials have confirmed the benefit of anticonvulsants such as carbamazepine (McQuay et al., 1995) and gabapentin (Backonja et al., 1998) and tricyclic antidepressants (McQuay et al., 1996), although the benefit of these drugs may be limited to about 30% patients reporting some improvement with each agent. The effectiveness of many of these drugs is often limited by side effects or intolerance (McQuay et al., 1996). Although there are no data on combination therapy, many of the participants in this study had tried various combinations of tricyclic antidepressants, carbamazepine, and NSAIDs without achieving sufficient relief of their symptoms. We set up the infusion program to offer these patients a further modality of treatment. As we were concerned that the apparent benefit of lignocaine therapy could be a placebo effect (caring environment, etc.), this trial in "lignocaine responders" was designed to objectively evaluate the effect of the drug.

We have shown that intravenous lignocaine at a dose of 5 or 7.5 mg/kg body weight will significantly reduce the experience of diabetic neuropathic pain in some patients with intractable symptoms who have been intolerant of, or unresponsive to, conventional therapy. Our findings using the widely accepted and independently validated MPQ are consistent with the only other published study (Kastrup et al., 1987) in unselected diabetic patients where response was assessed using an in-house symptom score and visual analog rating scales.

In our study, significant benefit was present 14 days after the infusion and persisted for up to 28 days. Lignocaine not only reduced the severity but also altered the qualitative features of the pain for up to 28 days after the infusion. The design of the study does not allow an assessment of the full duration of response to an infusion of lignocaine, but unexpectedly, it appeared to last at least 28 days. The pain relief clearly wore off to some extent in the next 14 days when active therapy (lignocaine of either dose) was followed by placebo (saline). There was a trend to a greater response to lignocaine at a dose of 7.5 mg/kg compared with 5 mg/kg, but this did not reach significance. This may either reflect a lack of power of the study or that the doses examined were near the top of the dose–response curve for lignocaine therapy.

The use of other medications to control pain did not differ between groups during the placebo and lignocaine

cycles of this study. The lack of difference in the hours of sleep and the daily pain scores between the treatments perhaps reflects the lack of sensitivity for these tests in assessing response to changes in pain intensity.

There is evidence that semiacute changes in blood glucose levels affect neuropathic pain (Archer, Watkins, Thomas, Sharma, & Payan, 1983). As there was no change in the mean fasting glucose between the three infusions cycles, improved glycaemic control seems an unlikely explanation of the reduced pain in this study.

As expected, lignocaine therapy was well tolerated in patients because all had previously received (and tolerated) at least four infusions in the regular program. One patient reported a headache during a lignocaine infusion at 7.5 mg/kg. Otherwise, neither patients nor the nursing staff were able to detect any response, either during or in the interval between the infusions, that may have inadvertently unblinded the study. While in our experience, intravenous lignocaine has been remarkably well tolerated, there is a brief report (Raphael, Southall, & Kitas, 2003) in patients with fibromyalgia receiving lignocaine, where 42% of participants experienced side effects. There were, however, significant differences in the dose schedule with the fibromyalgic participants receiving serial infusions for six successive days in contrast to the four weekly intervals of the current protocol.

One of the major limitations of our study was that the participants were not subjected to a full washout period between the different infusions. The participants were already part of a regular treatment programme with lignocaine and a full washout period was deemed unethical. As a result, it is not possible to delineate the duration or perhaps even the magnitude of benefit of lignocaine infusion for treatment of neuropathic pain. The observation that the previous dose of lignocaine in the study, whether higher or lower, affected the perceived response to the current dose reinforces the finding of the treatment benefit persisting for at least 28 days.

The conventional pharmacokinetics of intravenous lignocaine does not explain the prolonged benefit for up to 28 days. The central effects associated with high concentrations of lignocaine (sedation, ataxia, hypotension, and bradycardia) indicate that lignocaine may exert a central as well as a peripheral action. There are data to suggest that a least some of the neuropathic pain is generated by central (gating theory, spinal rewiring, or central spinal sensitisation) rather than peripheral nerve fibre or synapse abnormalities (Spruce, Potter, & Coppini, 2003). There may also be biotransformation of the lignocaine to metabolites with long half-lives (Chaplan, Bach, Shafer, & Yaksh, 1995). The mechanism for the prolonged effect observed here remains unexplained.

We have found that intravenous lignocaine administered over 4 h in a dose of 5 to 7.5 mg/kg provides relief from intractable diabetic peripheral neuropathic pain for up to 28 days. Further studies are required to establish the optimal dose and frequency of infusions. In our experience, this treatment has been remarkably free of side effects in our selected study patients.

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## References

Archer, A. G., Watkins, P. J., Thomas, P. K., Sharma, A. K., & Payan, J. (1983). The natural history of acute painful neuropathy in diabetes mellitus. *Journal of Neurology, Neurosurgery, and Psychiatry*, *46*, 491–499.

Backonja, M. M., Beydoun, A., Edwards, K. R., Schwartz, S. L., Fonseca, V., Hes, M., et al. (1998). Gabapentin for symptomatic treatment of painful neuropathy of patients with diabetes mellitus. *Journal of the American Medical Association*, *280*, 1831–1836.

Bril, V. (2001). Status of current clinical trials in diabetic polyneuropathy. *Canadian Journal of Neurological Sciences*, *28*, 191–198.

Chaplan, S. R., Bach, F. W., Shafer, S. L., & Yaksh, T. L. (1995). Prolonged alleviation of tactile allodynia by intravenous lignocaine in neuropathic rats. *Anesthesiology*, *83*, 775–785.

Cohen, K. L., & Harris, S. (1987). Efficacy and safety of non-steroidal anti-inflammatory drugs in the therapy of diabetic neuropathy. *Archives of Internal Medicine*, *147*, 1442–1444.

Dejgard, A., Peterson, P., & Kastrup, J. (1988). Mexiletine for the treatment of chronic painful diabetic neuropathy. *Lancet*, *2*, 9–11.

Diabetes Control and Complications Trial (DCCT) Research Group. (1995). Effect of intensive diabetes treatment on nerve conduction in the diabetes control and complications trial. *Annals of Neurology*, *38*, 869–880.

Dyck, P. J., Kratz, K. M., & Karnes, J. L. (1993). The prevalence of staged severity of various types of diabetic neuropathy, retinopathy and nephropathy in a population based cohort: The Rochester Diabetic Neuropathy study. *Neurology*, *43*, 817–824.

Eisenburg, E., Lurie, Y., Braker, C., Daoud, A., & Ishay, A. (2001). Lamotrigine reduces painful diabetic neuropathy. *Neurology*, *57*, 505–509.

Galer, B. S., Gianas, A., & Jensen, M. P. (2000). Painful diabetic polyneuropathy: Epidemiology, pain description and quality of life. *Diabetes Research and Clinical Practice*, *47*, 123–128.

Iacobellis, D., Allen, R., & Lamoreaux, L. (2000). A double blind, placebo-controlled trial of pregabalin for the treatment of painful diabetic peripheral neuropathy (Abstract). *Neurology*, *54*, A177.

Kastrup, J., Peterson, P., Dejard, A., Angelo, H., & Hilstead, J. (1987). Intravenous lidocaine infusion: A new treatment for chronic painful diabetic neuropathy. *Pain*, *28*, 69–75.

McQuay, H. J., Carroll, D., Jadad, A. R., Wiffen, P. J., & Moore, R. A. (1995). Anticonvulsant drugs for the management of pain: A systematic review. *British Medical Journal*, *311*, 1047–1052.

McQuay, H. J., Trammer, M., Nye, B. A., Carroll, D., Wiffen, P. J., & Moore, R. A. (1996). A systematic review of antidepressants in neuropathic pain. *Pain*, *68*, 217–227.

Melzack, R. (1975). The McGill Pain Questionnaire; major properties and scoring methods. *Pain*, *1*, 277–299.

Oskarsson, P., Lins, P. E., & Ljunggren, J. C. (1992). Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. *Diabetes Care*, *20*, 1594–1597.

Raphael, J. I., Southall, J. L., & Kitas, G. D. (2003). Adverse effects of intravenous lignocaine therapy in fibromyalgia syndrome. *Rheumatology*, *42*, 185–186.

Spruce, M. C., Potter, J., & Coppini, D. V. (2003). The pathogenesis and management of painful diabetic neuropathy: A review. *Diabetic Medicine*, *20*, 88–98.

UK Prospective Diabetes Study (UKPDS) Group. (1998). Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and the risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*, *352*, 837–853.

Veves, A., Manes, C., Murray, H. J., Young, M. J., & Boulton, A. J. M. (1998). Painful neuropathy and foot ulceration in diabetic patients. *Diabetes Care*, *16*, 1187–1189.

Winters, D., Kast, S., Simpson, R., & Newnham, H. (1996). Lignocaine therapy for painful diabetic neuropathy (Abstract). Proceedings of the Annual Meeting of the Australian Diabetes Educators Association, Sydney.

Young, M. J., Boulton, A. J. M., McLeod, A. F., Williams, D. R., & Sonksen, P. H. (1993). A multi-centre study of the prevalence of diabetic neuropathy in the UK hospital clinical population. *Diabetologia*, *36*, 150–154.

Yuen, C. J. (2002). Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray, a double blind placebo-controlled cross-over study. *Diabetes Care*, *25*, 1699–1703.