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Diabetic Painful Neuropathy

Current and Future Treatment Options

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Abstract

Diabetic painful neuropathy (DPN) is one of the most common causes of neuropathic pain. The management of DPN consists of excluding other causes of painful peripheral neuropathy, maximising diabetic control and using medications to alleviate pain.

The precise relationship between glycaemic control and the development and severity of DPN remains controversial. In this context, drugs such as aldose reductase inhibitors, ACE inhibitors, lipid-lowering agents and α-lipoic acid (thioctic acid) may have a useful role to play. There is also evidence that a successful pancreatic transplant may improve symptoms over time, but the mainstay of management continues to be symptomatic control of pain with drugs.

Evidence from placebo-controlled studies has shown that opioids, antiepileptic and antidepressant drugs together with capsaicin are effective for alleviating DPN. Tramadol and oxycodone have been shown to be effective in studies of limited

duration but their adverse effects, such as constipation and physical dependency, may limit their usefulness as a first-line treatment for DPN. Of the antidepressant drugs, the tricyclic antidepressants have been shown to be effective for alleviating DPN. These medications are widely used but their anticholinergic and sedative properties may not be well tolerated by patients. There is also good evidence that the serotonin-noradrenaline reuptake inhibitor antidepressant drugs venlafaxine and duloxetine are effective for treating DPN. However, venlafaxine may cause cardiac dysrhythmias, and patients using this medication require careful cardiac monitoring. Duloxetine appears to be less cardiotoxic and is licensed in the US and EU for alleviating DPN. The gabapentinoid group of drugs, gabapentin and pregabalin, appear to be the most evidence-based of the antiepileptic drugs for treating DPN. Large placebo-controlled studies have been performed with both of these agents. For many patients, it is still unclear what advantages pregabalin has over gabapentin for DPN. Until better evidence emerges, the potential availability of less expensive generic formulations of gabapentin, together with greater experience with its use, favour gabapentin as the main antiepileptic drug for alleviating DPN. Topiramate, lamotrigine, sodium valproate and oxcarbazepine have been shown to be effective in smaller studies but do not have the same evidence base as the gabapentinoid group of drugs. Of the newer antiepileptic drugs, lacosamide appears to be the most promising for alleviating DPN. Capsaicin has the best evidence base of all the topical agents, but local anaesthetic patches may also have a useful therapeutic role.

It is not possible to nominate a single drug as the first-line treatment for DPN and there is evidence that a low-dose combination of two or more drugs rather than a single agent may provide better symptomatic relief with fewer adverse effects. Further studies are necessary to clarify the best combination(s) of treatment for DPN.

Diabetes mellitus and glucose intolerance can cause painful radiculopathy, plexopathy and multiple mononeuropathies that are of acute onset and self-limiting. However, the most common painful diabetic neuropathy affects the periphery, causing a glove and stocking pattern of sensory loss as well as affecting the autonomic nerves, and leading to a chronic pain syndrome usually termed diabetic painful neuropathy (DPN).

Symptoms and signs of peripheral neuropathy may be found in up to 60% of diabetic patients but not all patients experience pain.[1] The prevalence of DPN in a community-based study was reported to be 16%.[2] In the same study, the prevalence of painful peripheral neuropathy in matched non-diabetic patients was around 5%. Evidence from other studies suggests that a substantial number of these patients with 'idiopathic' painful peripheral neuropathy may have impaired glucose tolerance and many will develop frank diabetes over time.[3,4] Pain may be the first symptom in this group of patients, and the presence of neuropathic pain should lead to further investigation. A glucose tolerance test would confirm the diagnosis, and early treatment may avoid the late complications of prolonged hyperglycaemia. In future, the number of patients with glucose-intolerant painful neuropathy will probably rise as a consequence of the increasing worldwide levels of obesity. The rate of increase may be even greater than that of patients with type 2 diabetes. For practical purposes, the management of these patients (although not strictly diabetic) is the same as for those with DPN.

The pathogenesis of DPN is complex. Apart from metabolic changes and vascular insufficiency, there is also evidence of alterations in growth factor and membrane channels in the peripheral nerves of diabetic patients (see review by Gooch and Podwall[5]). The objective of this article is to review the current literature and to provide an evidence-based approach to managing diabetic painful neuropathy.

1. Diagnosis of Neuropathic Pain

Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system".[6] It may be central or peripheral in origin.

The diagnosis of peripheral neuropathic pain is based on the history of pain, which may be spontaneous, continuous or intermittent, often worse at the end of the day, localised to one or more dermatomes, and is described as burning, stabbing, tingling, numb, hot, cold or itching.[7] Examination may reveal sensory abnormalities with diminution of touch, pin prick sensation, hot and cold perception, or heightened perception, with or without allodynia (non-nociceptive stimulation perceived as painful) and hyperpathia (perception of incremental pain with continual stimulation). Neuropathic pain scales such as the Leeds Assessment of Neuropathic Symptoms (LANSS) Pain Scale[8] and Neuropathic Pain Scale[9] have been devised to aid the diagnosis, but they are not widely used by clinicians. Peripheral nerve conduction tests may be performed, but in DPN may show no abnormality. This is because in the physiological and even most pathological states, pain and nociception are mediated by small myelinated and unmyelinated peripheral afferent fibres. Nerve conduction studies predominantly measure large diameter nerve conduction velocities. For the same reason, many diabetic patients may have abnormal neurophysiological test findings yet remain asymptomatic. Thermal thresholds in isolation or as part of quantitative sensory nerve testing[10] may be more appropriate indicators of dysfunction of small diameter sensory nerve fibres but are not widely available. Nerve or skin biopsies are useful only where the aetiology is unclear or for research purposes.[11] Therefore, for practical purposes, DPN is a clinical diagnosis supported by more than one sign, symptom or, where available, investigation result.

2. Management of Diabetic Painful Neuropathy (DPN)

The first step in managing patients with DPN is to exclude other possible causes of painful peripheral neuropathy (see table I). Once the diagnosis has been confirmed, management can be divided into two main categories: treatment directed at the pathophysiology of painful diabetic neuropathy and symptomatic treatment for alleviating pain (table II). It is generally assumed that reducing the risk of developing a peripheral neuropathy will also reduce the risk of DPN and that this must therefore direct first-line management once the diagnosis has been confirmed. However, the evidence to support this assertion is mixed (see section 3).

3. Control of Diabetes Mellitus

Prolonged poor glycaemic control is the most important risk factor for development of all the complications of diabetes. In the Eurodiab IDDM (Insulin-Dependent Diabetes Mellitus) study, which included >3000 patients, poor diabetic control, high levels of fasting triglycerides and the presence of microalbuminuria were important risk factors for developing diabetic peripheral neuropathy.[12] However, a prospective study of >2500 patients reported no direct link between blood glucose levels, as measured by glycosylated haemoglobin (HbA_{1c}) values, and the development of DPN,[13] although a larger population-based study did show a link between

Table I. Causes of peripheral neuropathy that are commonly painful

Alcoholism
HIV infection
Paraneoplastic syndrome
Monoclonal gammopathy
Vitamin deficiencies
Amyloidosis
Drugs and toxins: vincristine, cisplatin, isoniazid, arsenic, thallium
Vasculitic neuropathy
Fabry disease

Table II. Practical management of diabetic painful neuropathy

Treat underlying condition and maintain function
Good glycaemic control
Treat hypertension: ACE inhibitor
Check and correct serum cholesterol level
Regular inspection of feet: avoid neuropathic ulcers
Refer podiatrist for foot care and advice on footwear
Exclude other causes of painful neuropathy
Alcohol consumption? Check γ-glutamyl transferase level
Diet history? Vitamin deficiencies: measure B_{12} and folate levels
Paraneoplastic disorder: antineuronal antibodies/serum protein electrophoresis
Vasculitic neuropathy: check erythrocyte sedimentation rate
Other metabolic disorders: check thyroid and renal function
Non-pharmacological measures
Reduce allodynia if present: bed cradle
Transcutaneous electrical nerve stimulation (if mechanical allodynia not present)
Non-pharmacological symptomatic pain relief
Pharmacological agents
Topical: capsaicin cream (if tolerated) or lidocaine (lignocaine) patch
Tricyclic antidepressants if no contraindication
Gabapentin or pregabalin
Duloxetine
Opioids (acute control or breakthrough pain)
Combinations of the above

hyperglycaemia and neuropathy.[14] It has been pointed out that HbA_{1c} is a measure of mean blood sugar and that deviations in mean blood glucose levels, as measured by continuous blood glucose monitoring, may be more important for the development of DPN.[15] Many other studies have shown that there is a link between glycaemic control and microvascular complications, including neuropathy, and it would be sensible to advise patients to rigorously control their blood glucose levels to reduce the risk of diabetic complications.

3.1 Aldose Reductase Inhibitors

Metabolism of blood glucose via the polyol pathway where aldose reductase is a key enzyme may be important in the development of diabetic neuropathy.[16] Therefore, blocking aldose reductase may reduce this risk of diabetic neuropathy. In a 1-year placebo-controlled study, the aldose reductase fidarestat has been reported to be superior to placebo for reducing pain as well as the progression of peripheral diabetic neuropathy.[17] Another aldose reductase, epalrestat, is licensed in Japan and in a post-marketing surveillance of >5000 patients, this medication was reported to cause improvement of subjective symptoms, including spontaneous pain, in patients with DPN.[18] In a 3-year study, epalrestat was effective in slowing down the development of neuropathy as measured by changes in median nerve conduction velocity compared with controls. However, there was no significant difference in pain between treated and untreated group.[19] None of these medications is currently licensed in the UK or the US.

3.2 ACE Inhibitors and Lipid-Lowering Agents

The ACE inhibitor trandolapril was shown in a placebo-controlled study to improve peripheral neuropathy even in normotensive patients with diabetes.[20] In general, the ACE inhibitor class of medications appears to have some protective effect against microvascular complications and organ damage from diabetes.[21]

There is also evidence for a role of lipid-lowering agents in preventing DPN.[21] As mentioned in section 3, hypertriglyceridaemia has been found to be a risk factor for development of diabetic neuropathy. The lipid-lowering HMG-CoA reductase inhibitors (statins) may also possess neuroprotective properties in their own right.[22] Whether this class of medications can reduce microvascular complications in general and DPN in particular is unclear.

3.3 α-Lipoic Acid (Thioctic Acid)

α-Lipoic acid (thioctic acid) is a potent antioxidant that has been shown in numerous studies to improve signs and symptoms of diabetic neuropathy. In a meta-analysis of four placebo-controlled studies that randomised >1200 patients, α-lipoic acid 600 mg/day was reported to lead to an improvement in total symptom score in patients with diabetic neuropathy.[23] Both pain and burning were components shown to be improved in the group prescribed active treatment when compared with patients receiving placebo. The disadvantage of α-

lipoic acid is that it must be given intravenously. In the ALADIN (Alpha-Lipoic Acid in DIabetic Neuropathy) III study, there was no difference in symptoms between patients who were administered oral α-lipoic acid or placebo after both groups received an initial 3 weeks of intravenous active treatment.[24] A later study using dosages of oral α-lipoic acid ≤1.8 g/day appears to show that this drug may be effective for alleviating some neuropathic symptoms.[25] α-Lipoic acid is licensed in Germany, but not in the UK or the US, for the treatment of DPN. However, it is sold as a food supplement in both countries.

3.4 Transplantation of the Pancreas

Pancreas transplantation is the only therapy known to re-establish endogenous insulin secretion responsive to normal feedback controls in diabetic patients. In one series of 26 patients, neurophysiological examinations were performed before, 3 months and 12 months after a kidney and pancreas transplant.[26] All patients showed an increase in conduction velocity and amplitude of action potentials after 1 year, although the improvements took time to develop. There is anecdotal evidence that painful neuropathy improves after successful transplantation.[27] This may be an appropriate treatment for diabetic patients with renal failure in whom combined kidney and pancreatic transplants can be carried out. For many diabetic patients, this treatment option is limited by the shortage of donated organs, the complications of the procedure and the risks of long-term immunosuppression.

4. Non-Pharmacological Symptomatic Treatment

Simple measures such as using a bed cradle at night can alleviate the discomfort caused by the allodynia of DPN and may improve sleep disturbance. No systemic study of this method of pain relief has been performed but this seems a sensible initial step for patients with DPN to try. Transcutaneous electrical nerve stimulation (TENS) has been studied recently[28] in a small randomised double-blind study of 19 patients with mild-to-moderate DPN. In this study, pain, numbness and allodynia improved significantly in the group treated with TENS. A previous controlled study of 31 patients using electrostimulation versus sham stimulation also showed a positive result.[29]

There have been no large placebo-controlled studies evaluating the efficacy of acupuncture for DPN but small open-label trials have reported some benefit. Spinal cord stimulation has been reported to provide long-term relief for some patients with DPN but there have been no placebo-controlled studies and this is an expensive and invasive treatment.[30] It is not recommended as a routine procedure for treating patients with DPN.

Another more interesting non-pharmacological treatment is the possibility that transcranial magnetic stimulation might be effective in alleviating DPN. A placebo-controlled trial has shown that transcranial magnetic stimulation is effective for treating postherpetic neuralgia and central post-stroke pain.[31] Further trials are in progress.

5. Pharmacological Symptomatic Treatment

The drugs that are used for alleviating DPN can be broadly divided into two groups: (i) conventional analgesics such as tramadol and oxycodone; and (ii) adjunctive agents such as antidepressant and antiepileptic drugs (table III). The role of NSAIDs has not been extensively studied, but there is one short-term placebo-controlled study of 18 patients in which the active treatment was ibuprofen 2.4 g/day or sulindac 400 mg/day.[32] Both active treatments were reported to be superior to placebo. However, this class of medications is not widely used for this indication. Apart from this modest level of evidence for efficacy, high doses of NSAIDs also have the potential for exacerbating pre-existent renal impairment in patients with diabetes.

5.1 Measurement of Efficacy

The concept of number needed to treat (NNT) as a measure of efficacy of any treatment was first proposed by Cook and Sackett[50] in 1995. The NNT is calculated as the inverse of absolute risk reduction

Table III. Placebo-controlled studies with positive results in which >50 patients (pts) were randomised for alleviation of diabetic painful neuropathy (DPN)

Drug	Daily dose(s): active treatment (mg)	No. of pts	Outcome	Assessment: NNT values are for 50% pain relief (95% CI)	Reference
Opioids					
Tramadol	100–400 (mean 210)	131	Tramadol > placebo	Average mean pain intensity score (4-point scale): tramadol 1.4, placebo 2.2 Average pain relief score (4-point scale): tramadol 2.1, placebo 0.9 NNT 3.1 (2.1, 6.3)	33
Oxycodone	10–100 (mean 37)	159	Oxycodone > placebo	Average daily pain intensity (0–10 scale) 7 at randomisation: 4.1 for oxycodone and 5.3 for placebo at end of study	34
SNRIs					
Venlafaxine	75 150–225	244	75mg = placebo 150–225mg > placebo	150–225mg dose NNT 6.9 (3.7, 58.6)	35
Duloxetine	20 60 120	457	20mg = placebo 60mg > placebo 120mg > placebo	60mg NNT 4.3 (3.0, 9.2) 120mg NNT 3.8 (2.6, 7.2)	36
Duloxetine	60 120	348	60mg > placebo 120mg > placebo	60mg NNT 11 (4.7, ∞) 120mg NNT 5 (3.0, 13.0)	37
Duloxetine	60 120	334	60mg > placebo 120mg > placebo	60mg NNT 6.3 (4.7, 7.9) 120mg NNT 3.8 (2.1, 5.5)	38
Antiepileptic agents					
Gabapentin	≤3600	165	Gabapentin > placebo	NNT 4 (2.5, 9.6)	39
Sodium valproate (valproic acid)	1200	52	Sodium valproate > placebo	NNT 2 (1.0, 3.0) [but see comments Sindrup et al.[5,6]]	40
Lamotrigine	25–400	59	200–400mg > placebo	NNT 4 (2.1, 42.0)	41
Oxcarbazepine	≤1800	146	Oxcarbazepine > placebo	NNT 6 (3.3, 33.2)	42
Oxcarbazepine	600 1200 1800	347	Oxcarbazepine (all doses) = placebo on primary endpoint (mean visual analogue scale pain score)	NS	43
Topiramate	≤400	323	Topiramate > placebo	NNT 7.4 (4.3, 28.5)	44
Pregabalin	300	146	Pregabalin > placebo	NNT 3.9 (2.6, 8.7)	45

Continued next page

Table III. Contd

Drug	Daily dose(s): active treatment (mg)	No. of pts	Outcome	Assessment: NNT values are for 50% pain relief (95% CI)	Reference
Pregabalin	75	338	75mg = placebo	300mg NNT 3.6 (2, 5.2)	46
	300		300mg > placebo	600mg NNT 3.3 (2.5, 4.1)	
	600		600mg > placebo		
Pregabalin	150	246	150mg = placebo	600mg NNT 4.2 (2.7, 9.4)	47
	600		600mg > placebo		
Pregabalin	Fixed-dose 600	249 DPN	Pregabalin > placebo	Combined data for both groups of patients:	48
	Flexible-dose 150–600	89 post-herpetic neuralgia		Fixed-dose NNT 3.6 (2.4, 6.8) Flexible-dose NNT 4.2 (2.7, 9.3)	
Topical agents					
Capsaicin cream	0.075% cream qid	202	Capsaicin > placebo	Mean reduction in pain intensity: 40% capsaicin group vs 27.8% placebo	49

NNT = number needed to treat; **NS** = not significant; **qid** = four times daily; **SNRIs** = serotonin noradrenaline reuptake inhibitors.

for any treatment. McQuay and Moore[51] have refined and popularised this method of measuring treatment efficacy for chronic pain. These authors have conducted extensive systematic reviews and calculated the NNT as the inverse of the proportion of patients who achieve a given aim for any active treatment minus the proportion of patients taking placebo who achieve the same endpoint. Pain relief of >50% was their chosen endpoint.

The formula for calculating NNT is shown in equation 1:[51]

$$1\ (N_{active}/Total_{active}) - (N_{placebo}/Total_{placebo}) \qquad \text{(Eq. 1)}$$

where N_{active} = number of patients on active treatment achieving a defined endpoint; $Total_{active}$ = total number of patients on active treatment; $N_{placebo}$ = number of patients on placebo achieving a defined endpoint; $Total_{placebo}$ = total number of patients on placebo treatment.

The raw data necessary for calculating NNT can be derived only from randomised placebo-controlled trials in which the endpoints are clearly recorded. Once derived, the NNT is a useful way for estimating any active intervention for alleviating pain. However, it must be borne in mind that NNTs are not directly comparable between two different trials. The characteristics of the specific patient population that has been studied cannot be generalised to all patient groups. However, some of these variables may be diluted out by studies with large numbers of patients. Therefore, the numbers of patients studied is crucial and this information should be declared in any comparisons of different drugs.[52] The use of 50% pain relief as a measure for NNT is also an arbitrary measure. There is some evidence that 30% pain relief is clinically important when an 11-point numerical pain rating scale is used across many studies.[53] Despite these reservations, however, the NNT measurements as popularised by McQuay and Moore[51] remain an important step forward in the assessment of different therapeutic agents for alleviating pain.

5.2 Opioid Analgesics

Codeine and codeine/paracetamol (acetaminophen) mixtures have not been specifically studied in the treatment of DPN but are nevertheless widely used. It should be remembered that codeine is a prodrug that is metabolised to morphine in the liver, and that the pathway involved is subject to genetic polymorphism and up to 10% of the Caucasian population are unable to make the conversion.[54] This subgroup of patients would be expected to experience more adverse effects and less therapeutic effects with an equivalent dose of medication than patients who are fast metabolisers. Even for the majority of the population who are 'normal' codeine metabolisers, the usefulness of this medication may be limited by nausea, epigastric pain and constipation. In large doses and after prolonged use, codeine may cause tolerance and physical dependency. There is no evidence to support the prolonged use of codeine and codeine-like drugs for treating DPN and this practice should be discouraged.

In a randomised, double-blind, placebo-controlled study of >130 patients, tramadol at an average dose of around 200 mg/day for 6 weeks was shown to produce a statistically significant reduction in mean pain intensity in patients with DPN compared with those receiving placebo.[33] Secondary measures of physical and social functioning were also improved in patients receiving active treatment. Tramadol acts as a μ-opioid receptor agonist but also affects descending inhibitory pathways that modulate nociception, possibly by inhibiting presynaptic monoamine uptake and stimulating serotonin release. Theoretically, this is an advantage over other opioids for the treatment of neuropathic pain. However, higher doses (300–400 mg/day) are associated with a high incidence of adverse effects, such as drowsiness, nausea, headache and constipation, which limit the utility of this agent.

The other opioid that has been studied in a placebo-controlled fashion for treating DPN is oxycodone, which is an agonist at μ- and κ-opioid receptors. In one study of 159 patients, those receiving slow-release oxycodone at an average of 20 mg/day reported a reduction in average daily pain intensity of 1–2 points on an 11-point visual analogue scale compared with those receiving placebo.[34] Again, this was a 6-week trial and the range of oxycodone use was from 10 mg/day to 100 mg/day. In another placebo-controlled study, patients with DPN were randomly allocated to treatment with oxycodone or an active placebo in the form of benztropine 0.25mg.[55] The maximum dose of controlled-release oxycodone was 80 mg/day. This was a crossover study for a maximum of 4 weeks on each treatment arm with a washout period in between. Thirty-six patients were included in this study and, again, those receiving oxycodone reported significantly lower mean daily pain intensity compared with those receiving benztropine.

In conclusion, there is very good evidence from well conducted, placebo-controlled studies to support the use of tramadol and oxycodone for alleviating DPN. However, it is important to bear in mind that these trials were of only relatively short duration (6 weeks). The shift in visual analogue scores was significant, but small, with a reduction of two points or more being considered clinically significant. Other opioids may be as efficacious as tramadol and oxycodone for alleviating DPN but have not been studied. It is important to note also that long-term use of opioids may be associated with significant adverse effects, in particular the development of tolerance, so that higher doses of the drug are necessary to achieve the same degree of pain relief. Adverse effects of opioids include physical dependency, constipation, itching, alterations of immune function, impaired cognitive function and suppression of the pituitary axis. Therefore, opioids should not be prescribed to patients with a history of drug or alcohol abuse. Guidance on the use of opioids in non-malignant pain is available from the British Pain Society.[56]

5.3 Adjunctive Analgesics

Adjunctive analgesics for DPN consist predominantly of antidepressant and antiepileptic medications that have been shown to be effective for treating neuropathic pain in general and DPN in particular.

5.3.1 Tricyclic and Tetracylic Drugs

The tricyclic and tetracyclic drugs were initially developed for treating depression. They have numerous mechanisms of action including inhibition of noradrenaline and serotonin uptake from synaptic clefts. Different drugs from this class of medications also block anticholinergic receptors but to varying degrees. Lastly, amitriptyline, in particular, may also block sodium channels. In a meta-analysis of placebo-controlled studies of drugs for treating neuropathic pain, Sindrup and Jensen[57] identified one randomised controlled trial of amitriptyline and three randomised controlled trials of imipramine for the alleviation of DPN, which all favoured active treatment over placebo. In a pivotal study by Max et al.,[58] amitriptyline at an average dose of 90 mg/day was more effective than placebo for alleviating DPN. However, the number of patients randomised in this crossover study was only 29. Three small studies have been published comparing imipramine with placebo in double-blind, placebo-controlled, crossover designs for treating DPN.[59-61] The combined total number of patients randomised was <50, but imipramine at an average dose of 150–200mg was reported to be more effective than placebo.

There have been further trials of clomipramine[62] and desipramine[63] in placebo-controlled, crossover studies reporting that active treatment was more effective than placebo for alleviating DPN. Since then, tricyclic and tetracyclic drugs have been established as an important class of medications for alleviating DPN. The NNT computed from available data on tricyclic and tetracyclic drugs for DPN was 3.4 for one patient to achieve >50% pain relief.[59] This places tricyclic and tetracyclic drugs in a favourable light compared with other classes of medications. However, it is important to bear in mind that the sum total of patients with DPN studied in all these trials of tricyclic and tetracyclic drugs is <120.

5.3.2 Selective Serotonin Reuptake Inhibitors and Serotonin-Noradrenaline Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) block the reuptake of serotonin and noradrenaline released from pre-synaptic nerve terminals.

The study of SSRIs for treatment of DPN has been confined to a few small trials. In a crossover study of 48 patients, Max et al.[58] reported that fluoxetine 40 mg/day was no better than placebo for DPN. In another double-blind crossover study of 20 patients, paroxetine 20 mg/day was superior to placebo,[64] and in a further study of 15 patients, citalopram 40 mg/day was reported to be more effective than placebo.[65] However, the numbers of patients in these trials were small and these results should be interpreted with caution.

Since these results were published, there have been studies of the use of SNRIs in the treatment of DPN. In one of the larger placebo-controlled studies of 244 patients, slow-release venlafaxine 150–225 mg/day was more effective than placebo in reducing daily pain intensity as measured on a visual analogue scale.[35] The NNT for 50% pain relief at 6 weeks was 4.5. However, venlafaxine caused clinically significant ECG changes in at least seven patients. This is a potentially serious adverse effect that will limit the use of this medication, especially in diabetic patients who are susceptible to cardiovascular disease. Another SNRI, duloxetine, is now licensed for treating DPN in the US. Three large randomised placebo-controlled studies have reported its efficacy. In one 12-week, double-blind multicentre study of 457 DPN patients, duloxetine 60–120 mg/day but not 20 mg/day was more effective than placebo in relieving DPN.[36] Another study of similar design involving 348 DPN patients showed that patients treated with duloxetine 60 mg/day or 60mg twice daily reported significantly lower pain scores compared with patients receiving placebo.[37] In the third study, 334 patients were randomised to receive placebo or duloxetine 60 or 120 mg/day. Fifty percent reduction in average pain was reported by 27% of those receiving placebo, but by 43% of patients receiving duloxetine 60mg and 53% of those receiving 120mg daily.[38] Duloxetine appears to be well tolerated, with fewer gastrointestinal adverse effects than other SNRIs, and it may prove to be a very important adjunct in the treatment

of DPN. In the UK, duloxetine is now licensed for treating depression, urinary incontinence and DPN.

5.3.3 Antiepileptic Drugs

Phenytoin was one of the first non-sedating, sodium channel antagonists developed for treating epilepsy. Its other mechanisms of action include blockade of L-type mediated Ca^{2+} current, inhibition of NMDA response, depression of basal intra-neuronal levels of cyclic guanosine monophosphate and increased neuronal GABA concentration. Two crossover studies of phenytoin for the treatment of DPN were conducted in the 1970s. In these studies, phenytoin at dosages of ≤300 mg/day was reported to be more effective than placebo for alleviating DPN in the 5-week study[66] but not in the 20-week study.[67] In patients with epilepsy, long-term treatment with phenytoin is now known to be associated with the development of osteoporosis, peripheral neuropathy and cerebellar ataxia. Regular blood count measurement and liver function monitoring are also necessary in this context. Phenytoin is also highly protein-bound and has many potential interactions with other prescribed medications. For all these reasons phenytoin is not generally used for treating DPN.

Carbamazepine is thought to work primarily by blocking voltage-sensitive sodium channels in a use-dependent manner, reducing the ability of a neuron to fire repetitively at high frequencies. Its ability to block L-type Ca^{2+} and NMDA currents as well as increasing the release of serotonin may contribute to its efficacy for alleviating neuropathic pain. Finally, carbamazepine also antagonises adenosine A_1 receptors, which are important in nociceptive transmission. Only one major trial of carbamazepine, conducted in the 1960s, has investigated the efficacy of this agent in the treatment of DPN.[68] This was a crossover study that involved 30 patients. Carbamazepine between 200 mg/day and 600 mg/day was reported to be more effective than placebo in alleviating DPN. However, when prescribed for treating epilepsy, carbamazepine is known to be associated with bone marrow suppression and osteoporosis. This, together with the development of newer antiepileptic drugs, has superseded its use in the treatment of DPN.

Use of antiepileptic drugs for DPN increased dramatically following the introduction of gabapentin. The gabapentinoids bind to the $\alpha 2\delta$ site of L-type voltage-gated calcium channels and modulate the influx of calcium during neuronal depolarisation. In a widely publicised placebo-controlled study, gabapentin ≤3.6 g/day was reported to be more effective than placebo for treating DPN.[39] There were 165 patients randomised in this study and the calculated NNT for 50% pain relief for gabapentin was 3.7. This was an important study because, for the first time, a large placebo-controlled study involving >100 patients was conducted and the results were unequivocal that gabapentin is effective in alleviating DPN. Other studies have supported these findings and have prompted numerous other open-labelled studies and case series of gabapentin for alleviating neuropathic pain (for a summary of these studies, see Mellegers et al.[69]). However, gabapentin is licensed for treating postherpetic neuralgia only in the US. In the UK, gabapentin has a broad licensed indication for treating 'peripheral neuropathic pain' and is extensively used for alleviating DPN.

Sodium Valproate (Valproic Acid)

The mechanism of action of sodium valproate is to increase GABA levels *in vivo*, block T-calcium channels and increase neuronal potassium conductance at high concentrations. Sodium valproate is one of the older antiepileptic drugs, but there is some evidence of its efficacy for treating DPN. Fifty-two patients were randomised in a double-blind placebo-controlled trial for up to 3 months.[40] Although patients receiving active treatment reported a significant reduction in daily pain scores, more information is necessary to properly analyse the efficacy results of this study.[70] In practice, treatment with sodium valproate is associated with weight gain and hair loss in many but also liver toxicity in a small minority of patients. In older patients, use of sodium valproate has been reported to be associated with Parkinsonian symptoms. Children exposed to sodium valproate *in utero* are at risk

of developing neural tube defects and cognitive impairment. For all these reasons and the modest evidence of its efficacy, sodium valproate is not widely used for alleviating DPN.

Lamotrigine

Lamotrigine acts predominantly by voltage and frequency-dependent blockade of sodium channels. Other important actions include blocking of CA^{2+} currents, altering presynaptic release of glutamate and aspartate as well as increasing brain GABA concentrations. There has been one initial placebo-controlled study of lamotrigine for the treatment of DPN.[41] In this study, 59 patients were randomised to lamotrigine at doses of 25–400mg or placebo each day over a 6-week period. The primary endpoint of pain intensity was reduced in patients receiving >200 mg/day of lamotrigine. However, the secondary endpoints, including the McGill Pain scores and Patient Disability Index, showed no greater improvement with lamotrigine than with placebo. The results of two placebo-controlled studies have also been recently published. Over 700 patients with DNP were randomised to placebo or lamotrigine in escalating dosages up to 400 mg/day. The primary endpoint of change in daily mean pain intensity was not statistically significant between the placebo and active treatment group. Some of the secondary endpoints favoured active treatment but the results were inconsistent and only seen at dosages >300 mg/day. The efficacy of lamotrigine for alleviating DNP is therefore only very modest.[71]

Oxcarbazepine

Oxcarbazepine is the 10-keto analogue of carbamezepine and works mainly by blocking sodium channels. It is chemically closely related to carbamezepine and would be expected to be effective for alleviating DPN. There are two reported double-blind, placebo-controlled studies of oxcarbazepine for DPN. The first was a 16-week trial in which patients were randomised up to a maximum of oxcarbazepine 1800 mg/day.[42] The study included 146 patients and the primary endpoint of average pain score, as measured on a visual analogue scale, was reduced in those receiving active treatment compared with those patients receiving placebo. The calculated NNT for 50% pain relief was six. Secondary endpoint measures of Patient Global Impression of Change and sleep disturbance were also improved for patients receiving active treatment. In another study, 347 patients were randomised to treatment with oxcarbazepine 1200 mg/day, 1800 mg/day or placebo.[43] No statistical significance was reported between the treatment groups in the primary endpoint but there was a trend towards better pain reduction with active treatment, especially in patients treated with the higher dose of oxcarbazepine. Oxcarbazepine was generally well tolerated without any serious adverse effects. More information from other studies of oxcarbazepine needs to be made available before this medication can be recommended for treating DPN.

Topiramate

Topiramate blocks activity-dependent, voltage-gated sodium channels, enhances the action of GABA, inhibits L-type voltage-gated calcium channels, acts presynaptically to reduce the release of glutamate and post-synaptically blocks kainate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) excitatory amino acid receptors. The initial three placebo-controlled trials of topiramate for treating DPN showed that it was no better in this respect than placebo.[72] A number of reasons were advanced to explain the results of these rather disappointing trials.[72] However, another randomised, double-blind, placebo-controlled study reported a positive result for topiramate.[44] In this trial, 323 patients with DPN were randomised to treatment with topiramate ≤400 mg/day or placebo. The NNT for 30% pain reduction for topiramate was 6.25. Secondary endpoints of sleep disturbance and worse pain intensity were also significantly improved by active treatment. Topiramate was also associated with a mean reduction in bodyweight of ≤2.6kg. In a subsequent open-label extension of this trial, involving 205 patients over a period of 26 weeks, topiramate ≤600 mg/day was reported to remain as effective for alleviating DPN.[73] One interesting finding was that patients initially randomised to placebo achieved less pain reduction than patients initially treated with topiramate. The conclusion would

therefore be that topiramate does have a role in treating DPN but also has significant adverse effects at higher doses, with rapid titration to high doses being especially associated with cognitive impairment, dizziness, somnolence and paraesthesia. Topiramate is also a weak inhibitor of carbonic anhydrase and may increase the risk of developing calcium stones in some patients. However, the side effect of weight loss can be of benefit in patients with diabetes.

Pregabalin

Pregabalin is another gabapentinoid and shares the same mechanism of action as gabapentin. At least six large placebo-controlled studies of pregabalin for alleviating DPN have been conducted. Like gabapentin, pregabalin modulates calcium channel activity by binding to the $\alpha 2\delta$ receptor site. The dosage ranges of these studies were from 150 mg/day to 600 mg/day. When data from the four studies[45-48] published to date are combined, pregabalin at 300 mg/day and 600 mg/day was significantly more effective in alleviating DPN than placebo. Over 1000 patients were studied for between 8 and 12 weeks. The NNT for pregabalin at 300–600 mg/day for 50% reported daily pain relief was between 3.3 and 4.1. The more predictable absorption and twice daily dose regimen of pregabalin may make it an easier drug to use, but adverse effects of altered mood, especially euphoria, have been reported. Rapid dose titration increases the risk of causing sedation and dizziness. At high doses, pregabalin has also been reported to cause ankle oedema and weight gain. Furthermore, abrupt discontinuation of pregabalin has been reported to cause cerebral oedema and encephalopathy.[74] Pregabalin remains one of the most extensively studied drugs for alleviating DPN. In the UK and the US, it is licensed for alleviating DPN as a class V controlled substance and use of this medication has a low level of anticipated complications.

Zonisamide

Zonisamide is an antiepileptic medication that was first licensed in Japan where there is extensive experience of its use. Zonisamide is a voltage-dependent sodium and T-type calcium channel antagonist. A small initial study involving 25 patients reported that zonisamide at a mean dose of 540 mg/day was effective in alleviating DPN.[75] However, a large number of patients receiving active treatment withdrew and the benefits of zonisamide were not statistically significant.

Levodopa

Levodopa has been used for the treatment of Parkinson's disease for many years, often in combination with either benserazide (co-beneldopa) or carbidopa (co-careldopa). These combinations of drugs increase intracerebral levels of dopamine. A study in which 25 patients with painful symmetrical diabetic neuropathy were treated with levodopa 100mg combined with benserazide, three times daily for 4 weeks, has been published.[76] Eleven patients were given identical placebo capsules. There was a significant difference in pain between the active treatment and placebo groups according to visual analogue scale measurement, which was performed every day. Levodopa is an interesting medication that might be useful for treating some patients with DPN. However, there is insufficient evidence so far to recommend its general use and a much larger placebo-controlled study is needed for further assessment.

5.4 Topical Agents

There is evidence that both topical isosorbide dinitrate[77] and local anaesthetics in the form of lidocaine (lignocaine) 5% patches[78] are effective for treating patients with DPN.

In a randomised, double-blind, placebo-controlled, crossover study, 22 patients with DPN reported significant reduction in pain, as measured by the visual analogue scale, while using isosorbide dinitrate spray compared with placebo.[79] There were virtually no adverse effects and a once-daily spray before bedtime appeared to be effective for these patients. Fifty percent (11/22) of the patients reported benefit and stated that they would prefer to continue with the spray, compared with only 18% (4/22) patients receiving placebo.

There have been numerous studies and case reports of topical lidocaine 5% patches being effective

for treating DPN.[78,79] However, no large-scale, double-blind, placebo-controlled studies have been conducted to date. No serious adverse effects of lidocaine patches have been reported and although there has been concern about the potential systemic effects of lidocaine, blood levels have never been high enough to cause problems. In one study, up to four lidocaine 5% patches were used for up to 18 hours each day.[79] Mild skin irritation caused by the patch was reported, but this was considered to be a rare adverse effect.

Capsaicin is an alkaloid derived from chilli peppers that acts on the transient receptor potential vanilloid 1 receptor. Repeated application of capsaicin is thought to desensitise the receptors, leading to depletion of the neurotransmitter substance P from primary afferent neurons. There has been one large placebo-controlled study that shows that capsaicin is effective in alleviating DPN.[49] The therapeutic effect of capsaicin was also found to be comparable to that of oral amitriptyline in a double-blind, multicentre parallel study.[80] Over 200 patients were recruited into this study. The adverse effects of amitriptyline were found to be greater than those of capsaicin. The main disadvantage of capsaicin application is the initial burning sensation that may persist for days; indeed, many patients are unable to tolerate this adverse effect. Capsaicin must be applied regularly over the entire painful area, at least three to four times daily for up to 6–8 weeks before optimal pain relief can be achieved.

Use of isosorbide dinitrate spray for DPN deserves further evaluation. In the UK, lidocaine 5% patches must be imported and are expensive. Capsaicin cream has been shown in placebo-controlled studies (even with active placebo) to be effective for DPN. These topical medications can be particularly useful in more elderly patients with DPN in whom multiple systemic medications are contraindicated or may cause adverse effects. It must be borne in mind that use of antidepressant and antiepileptic drugs may be associated with significant morbidity amongst the older population and topical agents should be used as the treatment of first choice in this setting whenever possible.

6. Future Drugs and Directions

Although drugs acting on NMDA receptors showed initial high promise, the nonspecific nature of the available antagonists have rendered them relatively ineffective for alleviating DPN. In a small study, dextromethorphan has been reported to be effective, but only at doses of up to 400 mg/day.[81] In a follow-up study of dextromethorphan, memantine and lorazepam as an active placebo, dextromethorphan, but not memantine, was reported to be effective in alleviating DPN.[82] A large study of memantine for DPN was reported in abstract form[83] and, although some therapeutic effect was seen, pain relief appeared to be at a much lower level of efficacy than seen with amitriptyline or gabapentin. Lacosamide, which is thought to work on NMDA receptors, has been shown in two placebo-controlled studies to be effective for treating patients with DPN.[84] The drug was generally well tolerated. Preliminary results of these two studies were presented in a symposium on the 11th World Congress on Pain, in Sydney (NSW), Australia in August 2005. Some information on these studies is also available on the website of the company that is developing this product.[84]

There is an ongoing study of cannabinoids in the form of an oral spray for treating DPN.[85] However, there has been a setback in this study with the ruling from a UK coroner that use of this medication contributed to the unfortunate demise of a patient.[86]

Capsaicin analogues are being developed. The main candidate is NGX/410, which is a pure form of synthetic capsaicin, also known as trans-capsaicin, and which is being developed for rapid topical absorption. This form of capsaicin may act much more rapidly and may not need as many applications to achieve the same effect as the natural alkaloid.

In a recent paper, Finnerup et al.[87] have attempted to develop an evidence-based algorithm for treating patients with neuropathic pain. In their analysis of the available evidence, tricyclic antidepressant drugs, followed by opioids and then the antiepileptic drugs gabapentin and pregabalin, provide the best evidence of being effective for treating neuropathic pain. SNRIs were excluded from the

recommended list possibly because the studies of duloxetine were not widely known at that stage.

Although these medications mentioned in the previous paragraph are effective, it remains unclear which is the best first-line treatment for patients with DPN. There have been few head-to-head comparisons and those that have been conducted tend to provide conflicting advice. For example, in a small head-to-head comparison of gabapentin 900 mg/day and 1800 mg/day or amitriptyline 25–75 mg/day, conducted in a double-blind crossover design and including 28 patients with DPN, both drugs were shown to provide adequate pain relief with no significant difference between the two.[88] The conclusion of the investigators was that gabapentin did not provide any advantage over amitriptyline. However, in an open-label study of gabapentin up to a maximum of 2400 mg/day and amitriptyline up to a maximum of 90 mg/day, gabapentin produced greater pain relief than amitriptyline and was also better tolerated with fewer adverse effects.[89] In a large open-label study, neither aetiology nor symptom analysis were correlated with pain relief when patients were treated with imipramine or gabapentin.[90]

The adverse effects of the medication may be the main deciding factor when choosing the initial treatment. Amitriptyline has anticholinergic effects, which are a relative contraindication in patients with glaucoma, prostatism and cardiac disease. Amitriptyline can also cause postural hypotension, and the sedative effect of tricyclic antidepressants has been linked to significant morbidity, particularly among the older population. However, this mild hypnotic effect can be usefully employed in some patients who have troublesome symptoms at night. Gabapentin can affect higher cognitive function and mood and, in large doses, result in weight gain. Early experience shows that pregabalin may also cause the same adverse effects, although the severity of these effects is less clear. There is no head-to-head comparison of gabapentin and pregabalin in the treatment of DPN and it is unclear whether pregabalin is more efficacious than gabapentin in this context. Pregabalin has a more consistent absorption pattern than gabapentin and is taken twice daily, whereas gabapentin is taken three times daily. Until further studies have been conducted, the potential lower cost of generic preparations of gabapentin together with greater experience with its use would marginally favour use of gabapentin over pregabalin in the UK. It should be noted that pregabalin is classified as a class V controlled drug in the US.

There is good evidence to support use of the analgesics tramadol and oxycodone for DPN but long-term use of opioids in patients with non-malignant pain has to be considered carefully. These drugs may be used to establish early pain control whilst introducing other more slow-acting drugs. Of the newer adjunctive analgesics, duloxetine appears to be effective without any potentially serious adverse effects. In women with stress incontinence and DPN, this must be the drug of choice. In more frail elderly patients with DPN who are least capable of tolerating the sedative adverse effects of systemically administered drugs, capsaicin cream would be the drug of choice. It is therefore a matter of choosing the appropriate drug for the particular patient, bearing in mind adverse effects and also cost, if one assumes the drugs are equally effective. The recent placebo-controlled crossover study of a combined approach using gabapentin and morphine seems to suggest that patients would prefer low-dose combinations of two medications rather than a higher dose of a single drug to alleviate their DPN.[91] Combination drug regimens are more difficult to study and may be more expensive. However, there is logic in using a direct analgesic to alleviate pain whilst taking time to titrate the dose of an adjunctive analgesic to achieve long-term pain relief. It is also possible that one drug may potentiate the therapeutic effect of another when used in combination. More studies of longer duration are necessary to determine the best combination regimens.

7. Conclusion

The large number of therapeutic agents that are discussed in this article indicates that none is completely effective in treating either the cause or the

symptoms of DPN. It is a distressing and disabling condition, and the search for effective therapeutic agents, either singly or combined, with minimal adverse effects, will continue. Prevention, early diagnosis and improvement of the treatment of diabetes will also play a significant role in reducing the secondary complications of this condition.

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