Managing painful neuropathy in diabetes

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Diabetes is growing in its prevalence. The International Diabetes Federation estimated 194 million people with diabetes in the year 2003; expecting to rise to 334 million by 2025 [1]. Up to a quarter of people with diabetes will develop painful diabetic polyneuropathy (PDPN) [2] and in one study 80% of the patients had moderate or severe pain [3]. Painful diabetic polyneuropathy is associated with significant morbidity and reduced quality of life. It is also associated with depression, sleep disturbances, and anxiety [4-7].

Successful treatment of PDPN can be difficult and requires a two pronged approach. Modification of the underlying disease with maintenance of euglycaemia [8,9] is most important along with pharmacologic treatment for pain relief. Classic analgesics such as paracetamol or non-steroidal anti-inflammatory drugs are not very effective in PDPN and other different classes of drugs have been studied for relief of pain with varying success [10].

Surveys have shown that there is substantial scope for improvement in clinical care. In a UK population based study 40% of patients with PDPN reported they had never received any treatment for the condition while a third had been prescribed drugs with no known efficacy in neuropathic pain [2]. Similar findings of inadequate treatment was found in two more recent European and American studies [6,11].

In order to evaluate the effects of pharmacologic management in PDPN, Wong et al. [12] identified 1231 citations of which 25 randomised controlled trials were chosen, following quality assessment. These studies were then assessed for efficacy and safety of anticonvulsants (traditional – carbamazepine, lamotrigine, sodium valproate, and newer generation – gabapentin, oxcarbazepine, pregabalin), antidepressants (tricyclic [TCA] – amitriptyline, desimipramine, imipramine, selective serotonin reuptake inhibitors – citalopram, serotonin noradrenaline reuptake inhibitor – duloxetine, Ion channel blocker – mexiletine, N-methyl-D-aspartate antagonist – dextromethorphan, opioid – controlled release oxycodone, tramadol) and topical treatments (capsaicin cream, isosorbide dinitrate spray) in comparison with placebo in 2984 patients.

Clinical success was defined as a 50% reduction in pain while withdrawal due to adverse events was a secondary outcome. The metanalysis found TCAs to be most effective (odds ratio [OR] 22.24), followed by traditional anticonvulsants (OR 5.33), newer generation anticonvulsants (OR 3.25), pregabalin (OR 3.96), citalopram (OR 3.5), duloxetine (OR 2.55), opioids (OR 4.25), and capsaicin cream (OR 2.37) in descending order. Withdrawals due to adverse events were significantly more common in patients receiving newer generation anticonvulsants (OR 2.98), duloxetine (OR 2.36), opioids (OR 4.06), capsaicin (OR 4.02) and nonsignificantly different from placebo in patients receiving TCAs and traditional anticonvulsants.

This study can be used as a guide for clinicians to select the appropriate treatment for patients with PDPN, but also highlights some of the challenges in clinical treatment. The efficacy of the drugs itself is limited: with the most efficacious drug in the meta-analysis, amitriptyline having an number needed-to-treat of 3. Adverse effects were not infrequent, and some drugs had greater OR for withdrawal due to adverse effects than the OR for 50% pain relief. Comparison of different trials in the metaanalysis is difficult due to the highly variable duration of treatment (between 2–16 weeks) which could influence the number of withdrawals. Most trials in the review were relatively short; with small number of patients and in certain drug groups the confidence intervals were large.

Treating PDPN must be multifactorial taking into consideration not only pain relief but also the underlying diabetes and appropriate glycaemic control is necessary. Other factors that need consideration are psychosocial, sleep, mood and quality of life issues. Anxiety or depression may be present and requires to be addressed [13]. Wong et al. [12] suggest TCA as firstline in pharmacological management. Unfortunately its side effects are not infrequent and contraindications include cardiac conduction disturbances as well as glaucoma.

The older generation anticonvulsants appear to be the next best step. However, this advice is based on clustering a group of anticonvulsants with very different modes of action. If they are analysed separately, the number of studies for each drug is relatively small and the evidence for efficacy does not seem convincing. The drugs with robust, well conducted randomised controlled trials are pregabalin, duloxetine, and gabapentin; all of which have been shown to be beneficial in treating PDPN. Therefore we would recommend use of these drugs as second line agents as they do not seem

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Received: February 20, 2008. **Accepted in final form:** April 3, 2008.
Declared conflict of interest: Edward B. Jude has received honoraria from Pfizer, and Boehringer Ingelheim.
Pol Arch Med Wewn. 2008; 118 (5): 260-261

to differ much in efficacy, but advising patients on the severity of side effects [10].

Treatment protocols should be devised locally keeping in mind drug availability and cost. Only one or two of these drugs should be included in the initial treatment protocol, so that clinicians can develop sufficient experience with them. However many patients will require multi-drug regimes and this can have an impact on adherence to treatment and drug-drug interactions and adverse effects all of which need to be borne in mind when setting up protocols. Personally we would use TCAs as first line if there are no contraindications e.g. cardiac; then adding in pregabalin or gabapentin. We would increase the dose to maximum recommended or the highest tolerated dose quite rapidly adding in the second drug few weeks after reaching the maximum dose of the first drug; if patients continue to experience painful symptoms. Patients not responding to these two treatments could then have an opiod based drug e,g. tramadol added to their regime. Ultimately discussing with the patient limitations of pharmacological therapy is important as not all patients will get complete pain relief from their PDPN.

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From the Editor

Synopsis: Wong M, Chung JWY, Wong TKS. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. BMJ. 2007; 335: 87-96.

In this systematic review with metaanalysis of 25 randomised controlled trials the authors assessed the efficacy and safety of anticonvulsants (traditional – carbamazepine, lamotrigine, sodium valproate, and newer generation – gabapentin, oxcarbazepine, pregabalin), antidepressants (tricyclic – amitriptyline, desimipramine, imipramine, selective serotonin reuptake inhibitors – citalopram, serotonin noradrenaline reuptake inhibitor – duloxetine, ion channel blocker – mexiletine, N-methyl-D-aspartate antagonist – dextromethorphan, opioid – controlled release oxycodone, tramadol) and topical treatments (capsaicin cream, isosorbide dinitrate spray) in comparison with placebo in 2984 patients with painful diabetic neuropathy. Pain was reduced by ≥50% or there was moderate relief of pain in patients receiving tricycylic antidepressants (OR 22.24), traditional anticonvulsants (OR 5.33), newer generation anticonvulsants (OR 3.25), pregabalin (OR 3.96), citalopram (OR 3.5), duloxetine (OR 2.55), opioids (OR 4.25), capsaicin cream (OR 2.37). Withdrawals related to adverse events were significantly more common in patients receiving newer generation anticonvulsants (OR 2.98), duloxetine (OR 2.36), opioids (OR 4.06), capsaicin (OR 4.02) and nonsignificantly different from placebo in patients receiving tricyclic antidepressants and traditional anticonvulsants. In patients with painful diabetic neuropathy anticonvulsants, antidepressants and opioids in comparison with placebo reduce pain, but are associated with higher frequency of adverse events. On the basis of indirect comparisons the authors suggest beginning treatment with capsaicin or tricyclic antidepressants, and in the presence of contradindications or inefficacy, the drugs should be given in the following order: sodium valproate or carbamazepine, pregabalin or gabapentin, duloxetine and opioids.

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