

## Diabetic neuropathic pain in the elderly

By Professor Gregory Peterson

Mr T is a slightly overweight, sedentary 68-year-old male with a 15-year history of type 2 diabetes.<sup>1</sup> He quit smoking 16 years ago and denies the use of alcohol. Mr T retired from a sales job three years ago. Other medical problems include hypertension and hyperlipidaemia. His medications are:

- Aspirin 100mg daily
- Atorvastatin 20mg daily
- Perindopril/indapamide 5/1.25mg daily
- Gliclazide 80mg twice-daily
- Metformin 500mg twice daily.

Approximately six months ago, he noticed a burning and tingling sensation in his feet. This has worsened and Mr T now described a burning, lancinating pain in both feet and ankles. He also felt that his sense of balance was diminished but thought it was merely a sign of ageing and was reluctant to see a doctor. He had no other symptoms. His blood pressure was 139/84 mm Hg, with a pulse of 78. Cardiovascular examination showed a regular rhythm and no murmurs. His physical examination was unremarkable except for some hyperaesthesia of both feet, as well as decreased vibratory sensation. Reflexes were normal and pedal pulses were palpable. Serum electrolytes were found to be normal, serum creatinine was 0.14mmol/L and the HbA<sub>1c</sub> was 7.8%. Mr T was diagnosed with peripheral diabetic neuropathy and commenced on carbamazepine 200mg twice-daily, and he subsequently reported that his burning and tingling sensation had started going away after taking the medication for only five days.

A 52-year-old man, Mr L presents with lower-extremity pain.<sup>2</sup> The pain is bilateral and is described as sharp and needlelike. The pain increases when he stands. He also experiences pain with any touch, including clothing, on his skin. The pain has been present for about seven months and is not relieved with paracetamol, with or without codeine. Mr L was diagnosed with diabetes nine years ago, and is currently on insulin and metformin therapy. His glycaemic control has been excellent recently, with his latest HbA<sub>1c</sub> being 6.2%. Mr L preferred to try a topical treatment and was commenced on capsaicin cream 0.075%, to be applied three times daily.

The previous article in this column discussed hypotension and its management in the elderly. A common cause of orthostatic hypotension in this patient group is underlying diabetes mellitus, via the complication of autonomic neuropathy, which can also be associated with diarrhoea, gastroparesis, impotence in males, and tachycardia and silent myocardial infarction.

Neuropathic pain is also a common consequence of long-standing diabetes, particularly if control is suboptimal. Up to half of diabetic patients will develop neuropathy, including autonomic neuropathy and sensory or painful neuropathy.<sup>3</sup> An estimated one in six diabetic patients experiences peripheral neuropathic pain.<sup>4-7</sup> Diabetic neuropathy is one of the commonest causes of peripheral neuropathy.<sup>6,8,9</sup> It is predominantly a disease of the older diabetic population, and shows a progressive course with limb amputation as the final possible end-point of the disease.<sup>10</sup>

*'Diabetic neuropathy is a debilitating and costly consequence of both type 1 and 2 diabetes.'*<sup>3</sup>

There is ample evidence to indicate that neuropathic pain impairs patients' mood, quality of life, activities of daily living and performance at work.<sup>11</sup> People with the condition have been found to generate 3-fold higher health care costs compared with matched controls.<sup>8</sup> Neuropathic pain is particularly problematic in that it is typically chronic, severe and aggravated by touch, and resistant to therapy with most conventional analgesics.<sup>7,9,11</sup>

Neuropathic pain may result from nerve-fibre injury or dysfunction of a single nerve (mononeuropathy) or multiple nerves (polyneuropathy). The most common type of diabetic neuropathy is a distal sensorimotor polyneuropathy in which symptoms tend to begin in the feet, then spread to the legs and fingers.<sup>5</sup> The damage typically develops insidiously as a painless loss or change of sensation that may be detected and quantified only by clinical tests.<sup>12</sup> Early detection is critical, since a preventive approach is the most effective way to avoid or postpone debilitating complications.<sup>13,14</sup>

Once established, painful diabetic neuropathy tends to be a symmetrical, burning type of sensation, often in the feet and ankles. The pain is typically worse at night and can be described as burning, stabbing, electric, pins and needles, shooting, aching, jabbing, sharp, cramping, tingling, cold, or allodynia (pain from normal touch).<sup>6</sup> Symptoms are





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variable, however, with some patients experiencing virtually unnoticeable pain for years, others experiencing gradual tingling and numbness, and some experiencing constant excruciating pain.

If the large sensory and motor fibres become affected, patients may become ataxic. The loss of sensation often associated with diabetic peripheral neuropathy can lead to neuropathic ulcers and, ultimately, to amputation.<sup>5,10</sup> Sensorimotor neuropathy is the primary risk factor for the development of diabetic foot ulcer, which is responsible for 85% of lower-extremity amputations in diabetic patients.<sup>12</sup>

*'Identification of peripheral diabetic neuropathy indicates a high risk of foot complications, such as ulcers and gangrene, often resulting in amputation.'*<sup>13</sup>

The primary cause of diabetic neuropathy is chronic hyperglycaemia,<sup>3,12</sup> which disrupts normal cellular metabolism in many complication-prone cell types and is especially damaging to neurons.<sup>3</sup> On a cellular level, excess glucose induces the formation of reactive oxygen species, reduces the neuron's ability to buffer free radicals and forms intracellular advanced glycation endproducts. At the tissue level, hyperglycaemia reduces the production of growth factors important for nervous system health, creates ischaemia by reducing blood flow and alters the extracellular matrix by the formation of advanced glycation endproducts.<sup>3</sup>

The age of the patient and duration of diabetes, along with cigarette smoking, alcohol consumption, hypertension, and hypercholesterolaemia are also independent risk factors for the development of diabetic neuropathy.<sup>12</sup>

Essentially, the treatment of diabetic neuropathy consists of achieving better glycaemic control and managing symptoms related to the neuropathy.<sup>6,10,16</sup> The available treatments for painful diabetic neuropathy are only modestly to moderately effective in relieving symptoms and are often limited by adverse effects and drug interactions.<sup>12</sup> The emphasis of management of diabetic neuropathy remains prevention by glycaemic control, given the clearly established relationship between hyperglycaemia and the development and severity of neuropathy. To date, the only treatment proven effective in preventing or slowing diabetic neuropathy is the control of diabetes itself.<sup>6</sup>

*'Treatments directed at symptom management are polypharmacy nightmares fraught with adverse effects and are only moderately effective.'*<sup>12</sup>

Painful diabetic neuropathy is best managed with a multifaceted approach.<sup>11,14</sup> Evidence supporting conservative non-pharmacological treatments (e.g. physiotherapy, exercise, transcutaneous electrical nerve stimulation and cognitive behavioural therapy or supportive psychotherapy) is limited; however, given their relative safety, these treatments should be considered whenever appropriate.<sup>11</sup> Simple analgesics (e.g. paracetamol and non-steroidal anti-inflammatory drugs) are usually ineffective in pure neuropathic pain.<sup>5,7,9,11</sup>

*'Neuropathic pain has long been recognised as one of the more difficult types of pain to treat. Despite the use of combination drug therapy, adequate pain relief in the elderly is difficult to achieve without adverse effects. In an attempt to minimise these it is important to include non-drug treatment options in the management plan.'*<sup>17</sup>

The pharmacological options for treating painful neuropathy include the tricyclic antidepressants, selective serotonin-reuptake inhibitors (SSRIs), some of the antiepileptic drugs, opioids, tramadol, and topical capsaicin (Table 1). There have been few head-to-head comparisons between the different agents, singly or in combination. What data is available generally favours tricyclic antidepressants over antiepileptic drugs and opioids.<sup>7,18,19</sup> Of the antidepressant drugs, the tricyclic antidepressants have been shown to be most effective for alleviating painful diabetic neuropathy.<sup>7,16,18</sup> Amitriptyline, desipramine (no longer available in Australia), imipramine, and clomipramine have demonstrated the best efficacy.<sup>12</sup> These medications are widely used but their anticholinergic and sedative properties may not be well tolerated. In general, the tricyclics should be used with extreme caution in the elderly because of the risk of adverse effects related to their ability to block muscarinic receptors (e.g. cognitive impairment, dry mouth, constipation, dizziness, blurred vision, and urinary retention) or  $\alpha_1$ -adrenergic receptors (postural hypotension). These effects are most pronounced with the tertiary amine tricyclics (e.g. amitriptyline, imipramine, clomipramine, and doxepin) and less with nortriptyline.



Table 1. General properties of some drugs commonly used to treat painful diabetic neuropathy<sup>11, 12</sup>

Drug/Drug group	Typical dosage (mg/day)	Some drug interactions	Some adverse effects
Tricyclic antidepressants	10-25 initially, increasing weekly as needed by 10-25, to 50-75	MAOIs, sedatives, anticholinergics	Dry mouth, sedation, confusion, urinary retention, constipation, postural hypotension
Venlafaxine	37.5 initially, increasing weekly as needed by 37.5, to 150-225	MAOIs, SSRIs, tricyclics, tramadol	Headache, sedation, insomnia, nausea, dry mouth, sexual dysfunction, hypertension
Paroxetine and citalopram	10 initially, increasing weekly as needed by 10, to 20-60	MAOIs, codeine, tricyclics, tramadol, dextromethorphan	Sedation, insomnia, dizziness, dry mouth, constipation, sexual dysfunction
Carbamazepine	200 initially, increasing weekly as needed by 200, to 1000-1600	MAOIs, phenytoin, tramadol, warfarin	Sedation, ataxia, confusion, fatigue, hyponatraemia, rash
Phenytoin	100 initially, increasing weekly as needed by 100, to 300-500	Carbamazepine, tramadol, SSRIs, amiodarone, warfarin	Sedation, ataxia, dizziness, confusion, gum hypertrophy, blood dyscrasias
Gabapentin	300-900 initially, increasing weekly as needed by 300, to 1200-2400 (reduce in renal impairment)	Antacids, CNS depressants	Sedation, ataxia, dizziness, dry mouth, weight gain
Pregabalin	50-150 initially, increasing weekly as needed by 50-150, to 300-600 (reduce in renal impairment)	CNS depressants	Sedation, ataxia, dizziness, dry mouth, weight gain
Tramadol	150 initially, increasing weekly as needed by 50, to 200-400	MAOIs, SSRIs, tricyclics, antiepileptics	Sedation, ataxia, dizziness, constipation, seizures
Mexiletine	150 initially, increasing weekly as needed by 50, to 600-1200	Other antiarrhythmic drugs, warfarin	Dyspepsia, headache, insomnia, tremor, ataxia, dizziness, dry mouth

There is also evidence that the serotonin-noradrenaline reuptake inhibitor venlafaxine is effective for treating painful diabetic neuropathy.<sup>7,16</sup> In general, however, the SSRIs are considered better tolerated but less effective than the tricyclics, and they should not be considered for monotherapy of diabetic neuropathy.<sup>5,7,12</sup>

Gabapentin and pregabalin appear to be the most evidence-based of the antiepileptic drugs for treating painful diabetic neuropathy.<sup>16</sup> The adverse-effect profiles of phenytoin, carbamazepine and lamotrigine also generally limit their use in neuropathic pain, especially in the elderly.<sup>5</sup> Gabapentin seems to have similar efficacy to amitriptyline in the treatment of peripheral diabetic neuropathy.<sup>16</sup> The most common adverse effects of gabapentin include somnolence, dizziness and, less commonly, gastrointestinal symptoms and mild peripheral oedema. Gait and balance problems, as well as cognitive impairment, may be worsened with gabapentin in the elderly patient. Pregabalin is better absorbed, but otherwise shares similar properties and, for many patients, it is unclear what advantages pregabalin has over gabapentin

for painful diabetic neuropathy. Pregabalin is more convenient in terms of being administered twice-daily, while gabapentin is generally dosed three times a day. Because they are renally excreted, the dosage of both drugs needs to be adjusted based on renal function, which will be reduced in elderly patients. Gabapentin should be started at 100mg daily in older frail people and those with renal impairment, and the dose increased every few days to achieve symptomatic relief of pain.<sup>7</sup> Caution is also needed with pregabalin in the old and frail, and a slow increment from 75mg daily to 75mg twice a day by the end of the first week is likely to be best tolerated. Patients rarely want to exceed 150mg twice a day because of the somnolence and dizziness common to antiepileptic drugs, plus blurred vision and oedema.<sup>7</sup>

*'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 painful diabetic neuropathy.'*<sup>16</sup>



Currently, there is little published information supporting the long-term efficacy of opioids in controlling neuropathic pain. The main role of opioids is in patients who have not responded to other treatment options.<sup>7</sup> Tramadol and oxycodone have been shown to be reasonably effective in studies of limited duration but their adverse effects, such as constipation, dizziness, nausea, somnolence and physical dependency, limit their usefulness as a first-line treatment for painful diabetic neuropathy.<sup>16</sup> The dosages need to be increased very slowly. In the case of tramadol, the dosage required for therapeutic effect in diabetic sensorimotor neuropathy is often relatively high (200-400mg/day).<sup>12</sup> Tramadol should be avoided in patients with a known history of seizures. Concomitant use of tramadol with SSRIs, tricyclic antidepressants, opioids, monoamine oxidase inhibitors (MAOIs), and neuroleptic medications can also increase the risk of seizures and serotonin syndrome.

Interestingly, dextromethorphan has shown modest benefit in diabetic peripheral neuropathy. Clinically, the extremely high average dosage required (almost 400mg/day) and the resulting adverse effects (e.g. sedation and dizziness) all but prohibit use.<sup>12</sup> Mexiletine and clonidine also possess limited evidence of efficacy in patients with diabetic peripheral neuropathy.

Capsaicin has the best evidence base, albeit rather limited, of the topical agents.<sup>14,16</sup> The chili pepper extract has the major advantage of avoiding systemic exposure and therefore the propensity to cause adverse reactions and drug interactions. It is generally well tolerated but can cause transient burning, sneezing, coughing and rash.<sup>19</sup> It is also relatively expensive.

The *Australian Therapeutic Guidelines* suggest the following first-line drug options for diabetic sensorimotor neuropathy:<sup>15</sup>

amitriptyline 25 to 150mg orally, nightly

or

carbamazepine 200mg orally, 2 to 4 times daily

or

gabapentin 300 to 600mg orally, 3 times daily

or

capsaicin 0.075% topically, 3 to 4 times daily.

It is noted that adverse effects in a significant proportion of patients limit the use of these agents. Because of the higher incidence of adverse effects with the tricyclic antidepressants, it is often argued that gabapentin could be recommended as the first-line drug in the elderly.<sup>17</sup> Evidence demonstrates that gabapentin is effective for diabetic sensorimotor neuropathy, but its use requires no less consideration and vigilance than more traditional medications, especially in elderly diabetes patients.<sup>12</sup> For elderly patients, gabapentin has the advantage of very few drug interactions. The obvious disadvantages of gabapentin are the relative cost and the divided dosing

regimen.<sup>12</sup> For treatment-resistant neuropathic pain, other antiepileptic drugs, mexiletine, tramadol or topical capsaicin could be cautiously introduced.<sup>17</sup>

In the elderly it is essential to start all medications for neuropathic pain at a low dose and gradually titrate up until a response is seen. Starting at too high a dose or titrating too quickly is likely to lead to poor adherence and failed therapy because of adverse effects. Because of this need for gradual dose titration, the pharmacist can help educate the patient that the onset of pain relief will be gradual. Some patients also need reassurance that treatment with antidepressants or antiepileptic drugs does not necessarily imply a diagnosis of depression or epilepsy.<sup>11</sup>

While many patients with diabetic neuropathy report intractable and severe pain, and better treatment strategies are clearly needed,<sup>11</sup> in many cases an intervention can have an enormous impact on the functionality of an elderly patient, even with only a small change in pain intensity, thus making the therapy a success.<sup>20</sup>

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