



National Prescribing Service Limited

**Case study 55 report:
Treatment options for
neuropathic pain**



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Case study 55

Treatment options for neuropathic pain

Scenario

Doris is a 64-year-old war widow with a 15-year history of well-controlled type 2 diabetes. She comes to you complaining of severe discomfort in her calves and feet.

Two months ago she noticed burning and tingling in both feet but put it down to cold weather and 'poor circulation', as her hands and feet have always felt 'cold and numb'. At times she recalled feeling 'electric shocks' through her legs, which have lately become more painful. She denies pain on walking and does not have lumbar pain or sciatica. She took maximum recommended doses of paracetamol for 4 days but stopped when it did not help. Over-the-counter ibuprofen resulted in stomach discomfort even when taken after food. She describes the pain now as 'someone jabbing pins and needles' into her. She would like your recommendation on treatments preferably subsidised by her 'gold card'.

She does not smoke but finds a glass of sherry before bedtime helps with her sleep, since the pain is worse at night and wakes her. She expressed concern about using 'narcotics' to control her pain, because of media reports about people abusing these medications and the potential for addiction.

She is currently taking metformin 500 mg three times daily and gliclazide 80 mg twice a day. On examination, her peripheral pulses and skin colour are normal. Blood pressure is 135/79 mmHg. Three months ago, glycosylated haemoglobin was 7% and total cholesterol was 4.8 mmol/L. Liver and renal function were normal, as were thyroid function tests and serum levels of vitamin B12.

1. What medication(s) would you recommend for Doris's pain at this visit? (If recommending multiple medications, list only one medication per line)

Medication

Starting dose and frequency

Reason for choice

2. a) Would you recommend non-pharmacological therapy for Doris's pain?

Yes No

b) If yes, please specify _____

3. a) How long after starting pharmacological therapy would you assess the effectiveness of the medication(s)?

b) How would you assess the effectiveness of the medication(s)?

c) If you used a pain scale in question 3b, please specify which pain scale you would use.

4. Doris returns 2 months later still complaining of pain despite being on the maximum tolerated dose of the medication(s) in question 1. What medication(s) would you recommend next? (If recommending multiple medications, list only one medication per line.)

Medication

Starting dose and frequency

Reason for choice

5. List 2 strategies or tips you would give to aid Doris in her adherence to her pain relief medication(s).

Summary of results

At the time of publication, 961 responses had been received. This report summarises responses from 200 general practitioners.

Case synopsis

Doris is a 64-year-old war widow with a 15-year history of type 2 diabetes well controlled on metformin 500 mg three times a day and gliclazide 80 mg twice a day. Two months ago she noticed burning and tingling in both feet, at times she recalled feeling 'electric shocks' through her legs which has lately become more painful. She describes the pain now as 'someone jabbing pins and needles' into her. She tried maximum doses of paracetamol for four days but stopped when it did not help. Over-the-counter ibuprofen resulted in stomach discomfort even when taken after food. (See page 3 for more details.)

Medications used at initial presentation of diabetic neuropathic pain

- For the initial treatment of Doris's diabetic neuropathic pain, 74% of respondents recommended amitriptyline.
- Of the 148 respondents who had recommended amitriptyline, 48% did so to be consistent with guidelines' recommendations (i.e. *Therapeutic Guidelines, Australian Medicines Handbook*).
- 21% of respondents recommended a combination of two medications, while 7% recommended a combination of three medications on the initial visit.

Assessing effectiveness of drug therapy

- 47% of respondents would assess the effectiveness of drug therapy 1–2 months after starting it.
- 86% of respondents would use a pain scale to assess the effectiveness of drug therapy. The most widely chosen pain scale by respondents (37%) was the Brief Pain Inventory.¹

Medications used in persistent diabetic neuropathic pain

- 67% of respondents would recommend gabapentin when Doris returned after 2 months of taking the maximum tolerated dose of the initial treatment without satisfactory pain relief.
- Many respondents gave similar reasons for their choice of medication (e.g. effectiveness, recommended therapy by guidelines, proven efficacy in major trials).
- Of the 135 respondents who recommended gabapentin on Doris's return visit, in 25% the rationale for this choice was its effectiveness and availability on the (Repatriation) Pharmaceutical Benefits Scheme.

Non-pharmacological therapy

- 86% of respondents would recommend non-pharmacological therapy for Doris's pain.
- Of the respondents recommending non-pharmacological therapy, 40% would recommend psychological support (e.g. stress-reduction management); 38% of respondents would recommend physical measures (e.g. transcutaneous electrical nerve stimulation).

Strategies and advice to manage the pain-relief regimen

- 28% of respondents would ensure that the patient and/or carer was aware of and knew how to appropriately manage adverse effects of the pain-relief medication(s), 20% would set realistic goals with their patients, and another 20% would use a multidisciplinary team approach (e.g. refer the patient to a pain clinic).

Results in detail

Medications used at initial presentation of diabetic neuropathic pain

Respondents were asked which medication(s) they would recommend as initial treatment for Doris's neuropathic pain. Table 1 summarises the main choices.

Seventy-two per cent of respondents would start with one medication at the initial visit, 21% would use a combination of two medications, and 7% would use a combination of three medications. (See Table 6 on page 10 for the most common combinations.)

When paracetamol, tramadol, oxycodone, or topical capsaicin were chosen, they were always recommended as part of a combined medication regimen.

Table 1	
Medication used for initial presentation	% of respondents* (n = 200)
Antidepressants	
Amitriptyline	74%
Nortriptyline	18%
Antiepileptic	
Gabapentin	10%
Pregabalin	4%
Carbamazepine	3%
Sodium valproate	2%
Simple analgesics	
Paracetamol	12%
Opioid analgesics	
Tramadol	3%
Oxycodone	1%
Topical preparations	
Capsaicin 0.075%	6%
Others (e.g. venlafaxine, doxepin, low dose aspirin, vitamin B12, alpha-lipoic acid)	3%

* Respondents may have more than one response



Practice points

- Manage neuropathic pain aggressively to reduce the risk of transition to persistent pain.^{2,3}
- Manage contributing factors to diabetic neuropathic pain (e.g. tight glycaemic control is effective in slowing the progression of diabetic neuropathic pain).⁴
- Start with one drug at a time and allow a trial period to assess response.⁵ (Refer to Practice points on page 7 for more details.)
- Start drug therapy with a tricyclic antidepressant (e.g. amitriptyline, nortriptyline) or an antiepileptic (e.g. gabapentin) shown to be effective in diabetic neuropathic pain.^{3,4}

Rationale for choice of therapy at Doris's initial visit

Many respondents gave similar reasons for their choice of medication(s) (e.g. effectiveness, well tolerated, familiarity with chosen therapy). Other reasons were specific to the medication (e.g. choosing a tricyclic antidepressant to aid sleep).

Amitriptyline was the most commonly recommended therapy at the initial visit; the main reasons given by respondents for this choice are shown in Table 2.

Table 2	
Reasons for choosing amitriptyline at the initial visit	% of respondents* (n = 148)
First-line therapy recommended by guidelines (e.g. <i>Therapeutic Guidelines, Australian Medicines Handbook, Therapeutic Goods Administration</i> ¹)	48%
Proven efficacy in trials	18%
Well tolerated	12%
Prescriber's familiarity with amitriptyline	8%
Cost of therapy	8%
Aids sleep	6%

*Respondents may have more than one response

¹The Therapeutic Goods Administration has not approved use of amitriptyline in neuropathic pain. However, tricyclic antidepressants have long been used to treat all forms of neuropathic pain.²



Practice point

Medications commonly used in neuropathic pain and their place in therapy for diabetic neuropathic pain are listed in the box below.^{3,5,6}

- Explain to patients, when relevant, that some medications are not approved by the Therapeutics Goods Administration or subsidised by the Pharmaceutical Benefits Scheme for neuropathic pain.

Medications commonly used in neuropathic pain and their place in therapy for diabetic neuropathic pain	
Amitriptyline	The most widely studied tricyclic antidepressant. Trial for 6–8 weeks (with at least 2 weeks at the maximum tolerated dose) before assessing response.
Carbamazepine	Limited evidence for use in diabetic neuropathy
Gabapentin	Effective alternative to amitriptyline or nortriptyline for initial treatment of diabetic neuropathic pain. Trial for 2 months before assessing response
Nortriptyline	Similar efficacy and trial period to amitriptyline. People who do not respond to amitriptyline may respond to nortriptyline. Nortriptyline is less likely than amitriptyline to cause hypotension, drowsiness and anticholinergic adverse effects, and so may be useful in the elderly
Opioids (including tramadol)	May be effective in the short term (1–10 weeks) for diabetic neuropathy but there are no data assessing efficacy, safety or effects on quality of life in chronic use of opioids in treating neuropathic pain
Pregabalin	May be as effective as gabapentin for diabetic neuropathic pain but has less efficacy and safety data. Consider pregabalin when amitriptyline, nortriptyline or gabapentin inadequately control pain. Trial for 4 weeks before assessing response
Topical capsaicin (0.075%)	May be useful if a tricyclic antidepressant (e.g. amitriptyline or nortriptyline) or a gamma-aminobutyric acid (GABA) analogue (e.g. gabapentin or pregabalin) is contraindicated or not tolerated
Tramadol	Adverse effect profile (e.g. central nervous system effects) and drug interactions limit usefulness. Reduce the dose of tramadol for people who have severe hepatic impairment or creatinine clearance < 30 mL/min
Venlafaxine and duloxetine	Limited evidence for use in diabetic neuropathy. Trial for 6–8 weeks (with at least 2 weeks at the maximum tolerated dose) before assessing response

Assessing effectiveness of drug therapy

Duration of trial before assessment of effectiveness

Respondents were asked how soon after starting drug therapy they would assess the effectiveness of therapy. Table 3 summarises the responses.

Table 3	
Time after initiation to assessment for effectiveness of drug therapy	% of respondents (n = 200)
4–8 weeks	47%
2–4 weeks	24%
1–2 weeks	14%
Less than 1 week	12%
Depending on the patient's response	3%

Methods for assessing effectiveness

Table 4 summarises the methods respondents would use to assess the effectiveness of drug therapy for Doris's diabetic neuropathic pain.

Eighty-six per cent of respondents would involve a pain scale in their assessment of drug therapy for Doris's diabetic neuropathic pain; 14% of respondents would not use a pain scale.

Table 4	
Methods of assessing the effectiveness of drug therapy	% of respondents* (n = 200)
Pain scale used	
Brief Pain Inventory (BPI) ¹	45%
Numerical scale (1–10)	29%
Visual analogue scale	12%
Others	
Interview patient	26%
Compare baseline subjectively	12%
Look through patient's pain diary	8%
Trial discontinuation of therapy	4%

*Respondents may have more than one response



Practice points

- Use a multidimensional tool if a pain scale is used (e.g. Brief Pain Inventory¹) because they provide more information about pain history, intensity and associated disability.⁷
- Discuss and agree on realistic treatment goals with the patient and carer. The goal of treatment should be to reduce symptoms to a tolerable level in order to maintain and restore function.⁸
- Confirm drug therapy is still effective by a trial of discontinuation using the same recording of outcome measures — this may be appropriate before continuing therapy for the long term.⁶

Doris returns 2 months later still complaining of pain despite using the maximum tolerated dose of the medication(s) you recommended for her initially. What medication(s) would you recommend next?

Medications used in persistent diabetic neuropathic pain

Fifty-two per cent of respondents indicated that they would use a combination of medications (see Table 6 on page 9 for the most common combinations):

- 40% of respondents would use a combination of two medications while 12% would use a combination of three medications.
- 32% of respondents would continue with the medication initially recommended in Question 1.

When respondents recommended topical capsaicin or an analgesic, they were always recommended in addition to another medication (e.g. gabapentin with paracetamol). Table 5 summarises the main choices.

Table 5	
Medications used at re-presentation when initial treatment offered inadequate pain relief	% of respondents (n = 200)*
Anticonvulsants	
Gabapentin	67%
Pregabalin	14%
Carbamazepine	7%
Sodium valproate	1%
Antidepressants	
Amitriptyline	27%
Nortriptyline	16%
Duloxetine	3%
Venlafaxine	2%
Topical preparations	
Capsaicin 0.075%	5%
Simple analgesics	
Paracetamol	3%
Conventional and COX-2 selective NSAIDs	3%
Opioids analgesics (including tramadol)	
Tramadol	4%
Oxycodone	4%
Morphine	3%
Buprenorphine patch	2%

* Respondents may have more than one response



Practice point

- Use combination therapy when pain relief with one drug is inadequate. Use drugs from more than one class to target the different mechanisms contributing to neuropathic pain.^{3,9}

Combination therapy and changes to initial therapy

The most commonly used combinations at the initial visit and representation are summarised in Table 6 below.

The most common changes made to Doris's initial therapy when she re-presents because of inadequate pain relief from the initial treatment are shown in Table 6.

Table 6	
Most commonly chosen medication combination	% of respondents (n = 200)*
At initial visit:	
Amitriptyline	
— with paracetamol	6%
— with gabapentin	4%
— with tramadol	3%
— with topical capsaicin	3%
— with paracetamol + topical capsaicin	2%
At re-presentation:	
Gabapentin	
— with amitriptyline	20%
— with nortriptyline	7%
— with tramadol	2%
Amitriptyline	
— with carbamazepine	5%
— with paracetamol and oxycodone	3%
At re-presentation: changes made to initial choice	% of respondents (n = 200)*
Initial drug remained the same	
Amitriptyline	
— gabapentin added	12%
— carbamazepine added	5%
— dose increased	4%
Gabapentin	
— amitriptyline added	7%
Amitriptyline with paracetamol	
— oxycodone added	3%
Initial drug(s) switched to another drug	
Amitriptyline → gabapentin	40%
Gabapentin → pregabalin	6%
Amitriptyline → nortriptyline	5%
Amitriptyline with paracetamol → gabapentin	4%
Nortriptyline → gabapentin	3%

*Only the top five responses are listed

Rationale for choice of therapy at re-presentation

Gabapentin was the most commonly recommended therapy for Doris's return visit; the main reasons given by respondents for this choice are shown in Table 7.

The reasons for the choice of other medications included good response rate as adjunctive therapy, possible efficacy from previous experience and aiding sleep.

Reasons for choosing gabapentin at Doris's re-presentation	% of respondents* (n = 134)
Effective and subsidised by PBS/RPBS [†]	25%
Proven efficacy in major trials	20%
Second-line therapy in guidelines (e.g. <i>Therapeutic Guidelines</i> , Therapeutic Goods Administration [TGA] [‡])	18%
Best available option	18%
Different mode of action to initial therapy	16%
Prescriber stated familiarity with gabapentin	6%
Others (e.g. increase pain threshold, cost, aid sleep)	5%

* Respondents may have more than one response.

[†] Gabapentin is RPBS authority listed for refractory neuropathic pain not controlled by other drugs.

[‡] TGA does not make recommendations for treatment options. TGA safeguards public health and safety in Australia by regulating medicines, medical devices, blood and tissues.

Practice points



- Make decision on which drug to use based on consideration of efficacy, adverse effects and cost.³
- Consider also other indications (e.g. need for sedation) or contraindications (e.g. cognitive impairment).³
- Start additional medications one at a time, at low doses and titrate as necessary to the maximum tolerated level.³
- Refer people who may require opioids (including tramadol) — because they have not responded to or cannot tolerate other drugs — to a pain specialist and/or a neurologist wherever possible.⁵
- When using analgesics:
 - titrate analgesic dosages against patient's responses and adverse effect and review regularly.⁸
 - give analgesics regularly for continuous pain relief (e.g. recommended dose of immediate release paracetamol to be given four times daily).⁸
 - start opioids at low doses and increase progressively over days. If patients do not respond to moderate doses, such as oxycodone 40 mg twice daily, they are unlikely to respond to higher doses.²
 - avoid tramadol in people who are taking drugs that increase the risk of serotonin toxicity (e.g. selective serotonin reuptake inhibitors) or reduce the seizure threshold (e.g. tricyclic antidepressants).⁸

Starting dosages for Doris’s neuropathic pain

Respondents were asked to give a starting dose and frequency for their recommended therapy for Doris. Table 8 is a summary of their responses for each of the most commonly chosen medications at Doris’s initial visit and at her return visit.

Table 8	
Common starting doses	% of respondents
Amitriptyline	n=162
10 mg at night	80%
25 mg at night	16%
Gabapentin	n=154
100 mg three times a day	82%
200 mg three times a day	10%
300 mg three times a day	5%
Nortriptyline	n=48
10 mg at night	85%
25 mg at night	10%
Pregabalin	n=36
75 mg at night	74%
75 mg twice a day	23%
Carbamazepine	n=20
100 mg twice a day	45%
100 mg three times a day	35%
200 mg twice a day	15%
Topical capsaicin 0.075%	n=16
Apply to the affected area at night	75%



Practice point

- Start at low doses and go slow. Adjust doses to patient’s response. Higher doses often have an increased risk of adverse effects.

Recommended starting dose ranges for diabetic neuropathic pain ^{5,8,11}	
Amitriptyline 10–25 mg at night	Gabapentin 100 mg three times a day
Capsaicin 0.075% topically, 2–4 times a day	Nortriptyline 10–25 mg at night
Carbamazepine 100 mg twice a day	Pregabalin 75 mg twice a day
Duloxetine 30 mg once a day	Venlafaxine 37.5 mg once a day

Non-pharmacological therapy for diabetic neuropathic pain

Most (86%) respondents indicated that they would recommend non-pharmacological therapy in conjunction with drug therapy; 14% of respondents would not recommend non-pharmacological therapy. Table 9 summarises the type of non-pharmacological therapy that respondents recommended.

Table 9	
Non-pharmacological therapy used to manage Doris's diabetic neuropathic pain	% of respondents (n = 172)*
Psychological support	
Stress reduction	18%
Cognitive behavioural therapy (CBT)	12%
Sleep hygiene	10%
Physical measures	
Transcutaneous electrical nerve stimulation (TENS)	14%
Exercise	9%
Cold water immersion	7%
Massage	5%
Acupuncture	3%
Referral to other health care professionals	
Physiotherapist	8%
Podiatrist	4%
Pain clinic	4%
Pain specialist	3%
Others (e.g. increase alcohol use, alpha-lipoic acid)	3%

*If respondents had more than one response, only the first response was included.



Practice points

- Consider non-pharmacological therapy as part of any management plan for neuropathic pain.¹⁰
- Refer patients whose pain relief is inadequate to a multidisciplinary pain clinic or palliative care service.⁵
- Provide patients with information about their conditions and resources about community support groups.³ The box below lists some available resources for patients experiencing diabetic neuropathic pain.

Diabetes Australia (www.diabetesaustralia.com.au) and the **US National Institute of Diabetes and Digestive and Kidney Diseases** (www.diabetes.niddk.nih.gov/dm/pubs/neuropathies/) provide information for people who have diabetic neuropathy.
The Neuropathy Trust (www.neurocentre.com) provides information for people who have neuropathic pain.

Strategies and advice to manage the pain-relief regimen

Respondents were asked to provide strategies or tips to aid Doris in managing her pain-relief regimen. Table 10 summarises the suggested strategies and advice the respondents would provide.

Table 10	
Strategies and advice to aid Doris manage her pain-relief regimen*	% of respondents (n = 200)*
Educate patients and/or carers:	
• ensure awareness and management of adverse effects	28%
• explain role and place of different medication(s)	16%
• explain the mechanisms of pain	10%
• provide consumer medicine information (CMI)	4%
Refer:	
• to a pain clinic (pain specialist, physiotherapist, psychologist, specialist nurse)	20%
• for Home Medicines Review (HMR)	16%
• to support groups (e.g. Diabetes Australia)	8%
• to a specialist other than a pain specialist (neurologist, endocrinologist)	3%
Set realistic treatment goals	20%
Combine non-pharmacological therapy with medication(s)	18%
Use a diary or log to record pain	16%
Provide lifestyle advice (e.g. sleep hygiene, avoiding triggers and regular exercise)	14%
Organise regular follow-up to assess efficacy and titrate doses	8%
Implement strategies to aid adherence [†]	7%
Reassure and counsel the patient (persistence with therapy, other options are available)	6%

*Each respondent provided two strategies

[†]Included using dosing administration aid [e.g. Dosette, Webster pack (3%)], using a medicine list to help set out when and how to take medication(s) (2%), or simplifying the medication regimen — dosing at same time(s) of day, once- or twice-daily dosing (2%).



Practice points

- Educate patients about diabetic neuropathic pain and its management.
- Provide specific information about dosing, precautions (e.g. potential drug interactions), and possible adverse effects and their management.
- Provide patients with consumer medicine information (CMI) leaflets: information about adverse effects of medicines is important although diabetic neuropathic pain may not be mentioned in the CMI.
- Discuss and agree on realistic treatment goals and plans for monitoring and follow-up.
- Ask patients to regularly record pain intensity, functioning levels and any adverse effects from drug therapy to aid monitoring of management.
- Suggest strategies to help people taking multiple medicines to adhere to drug therapy (e.g. a medicines list[‡]) and/or a Home Medicines Review.

[‡]Available at www.nps.org.au/medicines_list

Commentary 1

Key points

- The correct diagnosis of neuropathic pain is essential to select appropriate management approaches.
- Neuropathic pain can usually be diagnosed by a detailed patient history and a simple neurological examination.
- Antidepressants (tricyclics and serotonin–noradrenaline reuptake inhibitors) as well as gabapentin and pregabalin are the two first-line treatment options in neuropathic pain.
- Pharmacological management of neuropathic pain should be accompanied by education of the patient and/or carer and non-pharmacological treatment options such as psychological support and physical measures.

Case scenario

The case scenario of Doris is rather typical for the presentation of neuropathic pain and raises important issues with regards to this diagnosis.

In contrast to nociceptive pain, which is caused by actual or potential tissue damage, neuropathic pain, is caused by a lesion in the nervous system. A differentiation between nociceptive and neuropathic pain is essential, as the treatment differs significantly.

Of all the neuropathic pain syndromes, diabetic peripheral neuropathy is the most common in Australia; around one-fifth to one-quarter of patients with diabetes experience painful diabetic polyneuropathy.¹² This diabetic polyneuropathy can manifest as:

- autonomic neuropathy, with symptoms such as postural hypotension, loss of bladder control and erectile dysfunction
- focal neuropathy
- distal symmetrical neuropathy, as with Doris.

She describes the typical bilateral and symmetrical distribution in feet and hands (glove and stocking).

The diagnosis of neuropathic pain is often possible by simply listening to the description by the patient. As to be expected, Doris describes positive sensory signs and symptoms such as dysaesthesia, paraesthesias and spontaneous pain. In neuropathic pain these are often accompanied by negative sensory signs and symptoms such as loss of sensory quality, manifested as numbness and reduced sensation,¹³ pain occurs commonly in areas of numbness and sensory deficit.

In addition, patients usually use typical words such as electric-shock-like, stabbing, jabbing or pins and needles. In contrast to mechanical nociceptive pain, it is also common for neuropathic pain to be worse at night and to wake the patient up. For this reason neuropathic pain is often accompanied by other problems such as sleep deprivation; as in most chronic pain states, depression, anxiety and reduced quality of life are other consequences. In addition, in diabetic neuropathy the numbness can lead to the typical foot problems of the patient with diabetes.

Last but not least, the patient gives the diagnosis pretty much away by describing that neither maximum recommended doses of paracetamol for four days nor over-the-counter ibuprofen resulted in pain relief, as conventional analgesics are usually ineffective in the treatment of neuropathic pain.

Diagnosis of neuropathic pain

From the above paragraph, it becomes obvious that taking a careful pain history is often already sufficient to make an assumed diagnosis of neuropathic pain. As outlined above, type, distribution and location of pain are the important issues.

In addition, there are several specific diagnostic tools in the form of questionnaires available. The most commonly used are either the DN4 Diagnostic Questionnaire¹⁴ or the 'PainDetect' Pain Questionnaire.¹⁵ Both rely primarily on patient description and, in the case of the DN4,

of a number of simple bedside tests for sensory function and increased sensitivity. These questionnaires have been validated for neuropathic pain conditions and are a very useful screening tool.¹⁶

Simple bedside tests include a neurological examination, with an emphasis on sensory function, as well as tests for allodynia and hyperalgesia. Allodynia is defined as pain due to a stimulus that normally does not provoke pain; light manual pinprick or stroking the skin with a brush or cotton bud are simple techniques to identify allodynia. Hyperalgesia, an increased response to a stimulus that is normally painful, can be tested by manual pinprick.

Management of diabetic neuropathy

The options for managing diabetic polyneuropathy include, in principle, antidepressants (tricyclic antidepressants [TCAs] as well as serotonin–noradrenaline reuptake inhibitors [SNRIs]), gabapentinoids (gabapentin and pregabalin), the atypical centrally acting analgesic tramadol, and opioids such as oxycodone, morphine or methadone.

Most current treatment recommendations suggest starting treatment either with a TCA/SNRI or a gabapentinoid. Overall, TCAs are more effective and cheaper than gabapentinoids, but carry an increased risk of adverse effects.

Antidepressants

TCAs have always been the mainstay of neuropathic pain treatment, confirmed by excellent systematic reviews and meta-analyses, with numbers-needed-to-treat (NNTs) in the range of 2–3.¹⁷

Secondary amine TCAs such as nortriptyline and desipramine have fewer side effects but are similarly effective as tertiary amines (amitriptyline and imipramine). Sometimes amitriptyline is a good choice, as it also restores sleep if taken at night. Because of the potential cardiotoxicity of TCAs, these need to be used at the lowest effective dosage and should possibly be avoided in patients with ischaemic heart disease.

Specific problems develop in elderly patients, with increased rates of side effects, and the potential danger of suicidal or accidental overdose needs to

be appreciated. Starting these drugs at a low dose is strongly recommended. A starting dose of 25 mg of amitriptyline chosen by some respondents is clearly too high and will result in a lot of patients not continuing on this medication; 10 mg is a good starting dose, although I often recommend halving the tablets to 5 mg for the first few days. Dose should then be titrated slowly to effect and side effects, and most patients gain benefit in dose ranges of 25–100 mg at night. The effect of tricyclics in neuropathic pain develops over time; the respondents are correct to aim for an assessment period of 4–8 weeks.

Over the last few years there have been increasing reports showing that the SNRIs duloxetine and venlafaxine are well tolerated alternatives to TCAs in the treatment of neuropathic pain.¹⁸ Duloxetine doses of 30–60 mg at night and venlafaxine doses of 150–225 mg daily show similar effectiveness, with fewer adverse effects.

Gabapentinoids

Gabapentinoids bind to the alpha-2-delta subunit of the voltage-gated calcium channel in sensory nerves and thereby inhibit the release of excitatory transmitters such as glutamate and substance P. They have been shown to be effective in a wide range of neuropathic pain conditions, not only post-herpetic neuralgia and diabetic polyneuropathy, but also phantom-limb pain, Guillain-Barré syndrome, neuropathic cancer pain and spinal cord injury pain.¹⁸

The safety of these two substances, their rather low rate of adverse events and the lack of relevant drug interactions have made them first-line drugs for neuropathic pain in many guidelines.^{11,18,20} The problem in Australia is that they are not subsidised by the PBS, however, Doris has access to the Repatriation Pharmaceutical Benefit Scheme and thereby to financial support for this medication.

Again, titration to effect in consideration of adverse effects is the way to go. The onset of effect is usually rather fast but most literature would suggest a trial of 4–8 weeks. The advantage of gabapentin is the availability of a tablet with 100 mg, which makes slow titration, in particular in sensitive elderly patients, possible. It is often wise to start with a 100 mg dose at night then slowly build up to the effective dosage.

Disadvantages of gabapentin are the need for three-times-daily dosing and the poor correlation between dose and plasma concentration due to large inter-individual variability in bio-availability and saturable uptake kinetics. In my personal experience, I have patients gaining long-term benefit from 100 mg at night while other patients require 1200 mg three times daily.

Pregabalin has pharmacokinetic advantages with the option of twice-daily dosing, a linear dose–concentration relationship and titration is easier, as the maximum dose of 300 mg twice daily is more predictable; however, the smallest tablet size of 75 mg is often too strong to initiate titration in elderly people. Note that both compounds have anxiolytic effects in generalised anxiety disorder and this might be beneficial in some patients with neuropathic pain; gabapentin and pregabalin may also result in improved sleep and quality of life.

Opioids

Oral and transdermal opioids have proven efficacy in neuropathic pain that is similar to that of the TCAs and gabapentinoids. However, as opioids produce more adverse effects they are commonly regarded as second-line treatments for neuropathic pain. They should therefore be used in patients who have failed to respond to one of the first-line compounds or a combination of both groups or have shown intolerance to first-line compounds. Again, titration with opioids should be to achieve efficacy with minimal adverse effects.

A substance that might be specifically interesting in this group is the atypical centrally acting analgesic tramadol, which is only a weak opioid agonist but also an SNRI. It has shown efficacy in a variety of neuropathic pain settings, with an NNT in the range of 3.²¹ Further advantages are the lower abuse potential, the status as a non-S8 scheduled drug and a reduced rate and severity of constipation.

General considerations

The pharmacological management of neuropathic pain in diabetic neuropathy is long term and most likely lifelong. Therefore, slow titration to effect is an appropriate approach. If a treatment trial of sufficient duration with a first-line compound does not result in satisfactory

analgesia, it is logical to continue the chosen compound and add a representative of the other first-line medication. However, if side effects limit the use of the first-line medication of first choice, switching to another first-line medication is justified. Alternatively, combining any of the first-line treatments with tramadol or a low-dose opioid might be worth a trial, which might not necessarily require referral to a multidisciplinary pain clinic. Failure of first-line medications, even in combination with low doses of an opioid, should be the trigger for referral to a pain specialist or a multidisciplinary pain centre.

The option of topical treatment was considered by some respondents.²² Currently available in Australia is capsaicin 0.075%, which is useful with no systemic side effects, but often poorly tolerated due to local problems. A future option, already available in the US and Europe, are transdermal lignocaine plasters, which have shown efficacy in a range of localised neuropathic pain states.²³

As with all chronic pain management, the respondents are right to emphasise the non-pharmacological management options. Here explaining the disease and educating the patient and/or carer education regarding the planned medication and their adverse effects is essential. The agreement on realistic treatment goals, which are usually not complete analgesia, is important. In addition, it must be made clear that numbness and other dysaesthetic and paraesthetic components of diabetic neuropathy are usually non-responsive to treatment, and patients should be informed about that. Furthermore, the respondents correctly suggest that support in form of stress reduction improved sleep hygiene and physical measures should be considered.

Commentary 2

Crucial to good pain management is adequate monitoring of response to, and side effects of, treatment

Doris's case is typical of a diabetic pain presentation — that of peripheral vascular disease and neuropathic pain and sleep disturbance.

The choice of pharmacological agents depends on the needs of individual patients. For example, neuropathic pain warrants an adequate trial of an antiepileptic such as gabapentin. However, if the patient with diabetic neuropathic pain is principally depressed, a tricyclic antidepressant (TCA), or a serotonin–noradrenaline reuptake inhibitor (SNRI) (e.g. venlafaxine) would be warranted.

It is most important to start low and go slow and to give enough time and adequate dosage for efficacy to be assessed. This can only be done with regular review. This is why monitoring with the Brief Pain Inventory (BPI) is so important, as it not only assesses the pain (bio-) but also identifies the impact that neuro-pathic pain has on the patient (psycho/social).

The BPI identifies not only the severity of the pain but also enables both the doctor and patient to gauge the response to various medications and non-pharmacological options used to alleviate pain.

I have only one problem with the BPI — in Questions 2–6 it refers to 'your' pain. I find that giving the patient 'ownership' of the pain is not helpful. It is far better to refer to 'the' pain when talking to a patient about pain.

In Doris's case a single tricyclic antidepressant would address both the neuropathic pain and the sleeplessness. However, side effects and interactions need to be closely monitored, especially in older patients.

Respondents who chose to use two or more medications at Doris's initial visit (28%) would have difficulty identifying what is working or what is causing side effects. Introducing one medication at a time facilitates patient adherence and reduces the potential for drug interaction that could lead to adverse events. Therefore, stepwise introduction of drugs with close and frequent monitoring is a better option.

If a simple analgesic such as paracetamol lacked efficacy, starting an antiepileptic drug or an antidepressant would be required, depending on the patient's presentation. If, after an adequate trial on either of these medications, the pain persisted, the addition of a narcotic could be considered.

Whichever medication respondents chose at the first visit, my recommendation would be to assess effectiveness within the month. As most respondents chose to prescribe amitriptyline at the initial visit, I was surprised to see that 47% chose to wait from 4–8 weeks before 'assessing for effectiveness for drug therapy' after initiation.

Perhaps this reflects the workload of most GPs. From my experience, the expectation that patients would contact the surgery sooner if they had problems is not always the case. Mostly they stop taking the medications and the GP is none the wiser, especially if they have been told to return after a month on treatment.

When patients stop taking their medications without review or close supervision, because of a lack of efficacy or troublesome side effects, it becomes very difficult to know whether tolerance to the side effect(s) could have been achieved if these problems had been addressed sooner, or if a simple increase in dosage could have proven efficacious.

In the case of both amitriptyline and gabapentin, review would be required much sooner for dose adjustment and review of side effect(s). Even non-pharmacological measures such as lifestyle changes, pain diaries and sleep hygiene need regular monitoring.

Giving adequate time for response depends on the medication and the side effects experienced; for example, gradual increase in dose of gabapentin takes about 3 weeks to reach therapeutic efficacy. Adding a second medication, such as a narcotic, would then be considered. If a narcotic is used the patient and GP need to agree to a set period of treatment during which other physical measures should be considered and a tighter control of the blood glucose levels be instigated.

Realistic goal setting motivates the patient and enables the GP to measure outcomes. It is essential that patients focus on something

that gives them pleasure. They may wish to return to golf; however, 18 holes may be unrealistic whereas 9 could be the motivator that gets them up and going. At first interview I ask patients: 'What does this pain stop you from doing?' Their answers are most revealing and help me focus on meeting their needs.

Increasing patient adherence to therapy not only requires time but also help from ancillary services such as practice nurses, diabetic educators, dietitians and podiatrists. Reinforcing the message that regularly taking medications for pain is essential can be encouraged with the use of diaries and pain assessment tools by the patient.

Take-home message

Ensuring timely review to assess for efficacy and tolerability of pain management measures substantially improves outcomes in pain management.

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