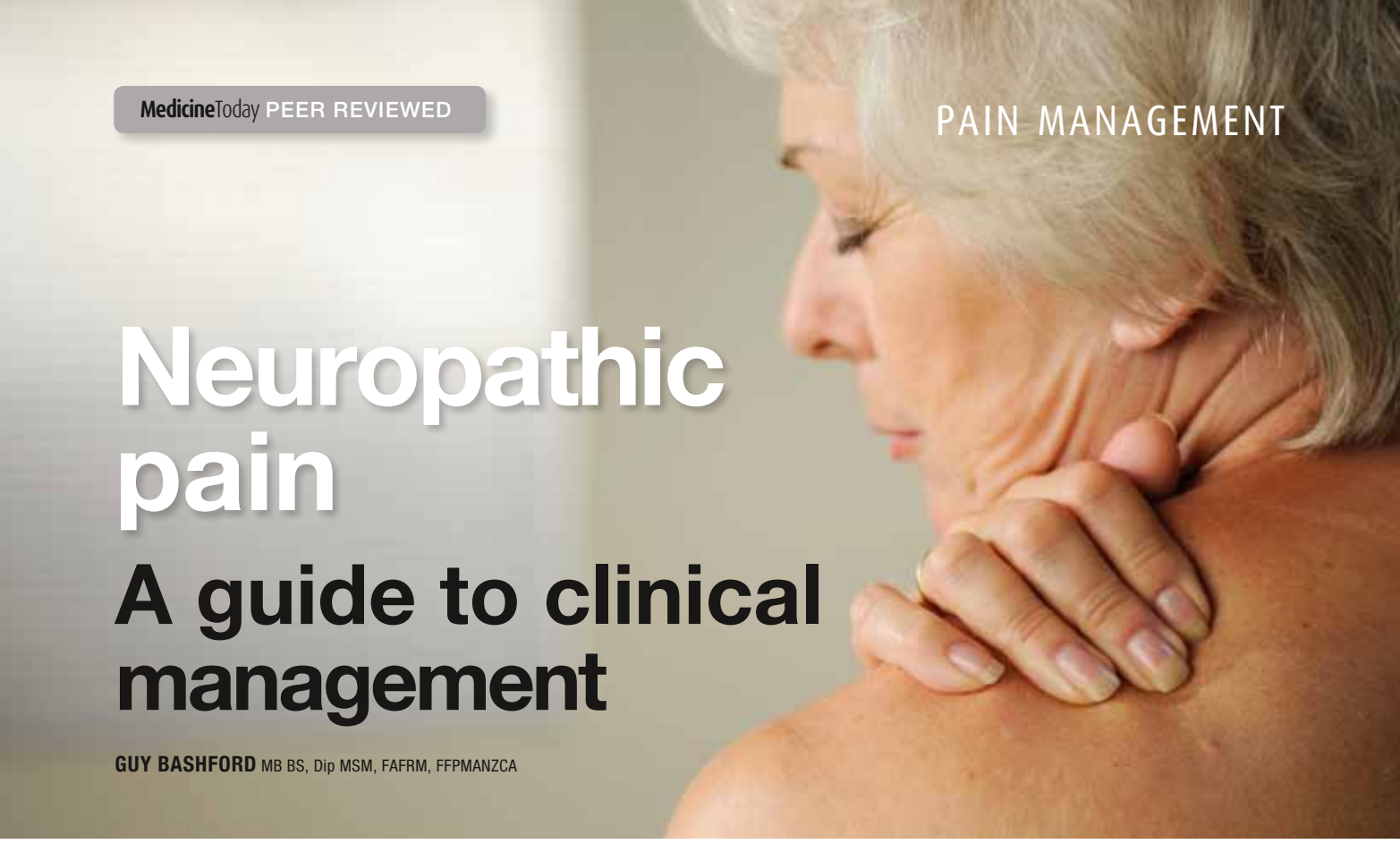

Neuropathic pain

A guide to clinical management

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Treatment selection for neuropathic pain depends as much on comorbid sleep disturbance, depression, anxiety and particularly in the elderly, medical comorbidities as on the pain itself.

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Most neuropathic pain in the community goes unrecognised and untreated. Even when patients and their general practitioners recognise neuropathic pain – defined as 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'[1] – they often adopt a nihilistic attitude to treatment. Many of the medications commonly used for nociceptive pain (pain caused by tissue damage or potentially tissue-damaging stimuli) are not effective in neuropathic pain. Likewise, many physical approaches for managing nociceptive pain may not be appropriate for neuropathic pain. Research into treatments for neuropathic pain has, however, expanded rapidly in the past decade, and there is growing consensus about management of this type of pain.

APPROACH TO MANAGEMENT

The first step in the management of neuropathic pain is recognising and diagnosing its presence; this was discussed in an article in the May 2013 issue of *Medicine Today*.[2] Common causes of neuropathic pain include sciatica, surgical nerve damage, diabetic neuropathy and postherpetic neuralgia. The diagnosis of neuropathic pain allows a concerted effort to educate the patient and their family about this pain. Without this education, distressing symptoms will likely be attributed to primary nociceptive or physical causes.

Not surprisingly, psychological and social comorbidities are generally more common in patients with neuropathic pain than in those with nociceptive pain. For instance, spontaneous pain is extremely common in neuropathic pain and is likely to disturb sleep. Selecting appropriate pharmacological and nonpharmacological management approaches for an individual depends as

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TABLE. TREATMENT OF NEUROPATHIC PAIN: RECOMMENDATIONS OF RECENT GUIDELINES*

Medication	Neuropathic Pain Special Interest Group (2007)[4]	European Federation of Neurological Societies (2010)[5]
Tricyclic antidepressants	First line	First line
Alpha-2-delta ligands (gabapentin, pregabalin)	First line	First line
SNRIs (duloxetine, venlafaxine)	First line for painful polyneuropathy	First line for painful polyneuropathy
Topical lignocaine	First line for localised peripheral neuropathy	First line for postherpetic neuralgia if small area of pain/allodynia
Opioid analgesics	Second line except in selected third-line circumstances	Second to third line for painful polyneuropathy, postherpetic neuralgia and central pain
Tramadol	Second line except in selected circumstances	Second to third line for painful polyneuropathy, postherpetic neuralgia

ABBREVIATION: SNRI = serotonin and noradrenaline reuptake inhibitor.
* Excluding treatment of trigeminal neuralgia and sciatica.

much on comorbidities such as sleep disturbance, depression and anxiety as on the pain. It is also influenced by the presence of other medical conditions, particularly in the elderly. It is therefore imperative that comorbidities are identified and their severity assessed before deciding on a specific drug or nondrug treatment approach for neuropathic pain.

DRUG TREATMENTS FOR NEUROPATHIC PAIN

Of the approximately 200 randomised controlled trials on neuropathic pain, around 60% were published within the past five years, and there is increasing agreement between evidence-informed treatment recommendations.[3-5] Recent guidelines for the treatment of neuropathic pain are summarised in the Table.

However, it must be recognised that the effects of proven medications are often disappointing, and their use at scientifically proven therapeutic doses may be limited by adverse effects. Complete resolution of neuropathic pain is very rare. Nevertheless, a 30% reduction in pain is likely to improve quality of life. It is important to ensure patients have realistic expectations before initiating treatment. They should understand that even with the best proven medications, only a quarter to a third of patients achieve pain relief of 50% or more.

Ineffective or unproven medications

Nearly all patients presenting with neuropathic pain will have tried paracetamol or an NSAID for their symptoms. There is no evidence that paracetamol is effective in neuropathic pain, except in combination with tramadol. There is also no evidence supporting the use of NSAIDs in neuropathic pain states.

Antidepressants

There is much evidence supporting the use of antidepressants with combined serotonin and noradrenaline reuptake inhibitory effects in neuropathic pain. Tricyclic antidepressants have been a mainstay of treatment for decades. There is level 1 evidence of their effectiveness in a variety of peripheral pain states (e.g. painful peripheral neuropathy and postherpetic neuralgia) and, to a lesser extent, central pain states (central spinal cord injury and poststroke pain).

The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain recommends a tricyclic antidepressant dose of 25 to 100 mg, where appropriate and safe.[4] The group also recommends a six to eight-week trial, which should include two weeks at the maximum dose. Achieving a therapeutic dose is often limited by side effects and safety, particularly in the elderly and those with cardiac or neurological comorbidities. The group recommends screening ECGs in all patients older than 40 years.

Side effects of tricyclic antidepressants are shown in the box on page 56. As these drugs cause sedation, with careful titration they can potentially improve sleep without causing troubling daytime drowsiness.

Serotonin and noradrenaline reuptake inhibitors (SNRIs; duloxetine and venlafaxine) have a safer and more tolerable side effect profile than a tricyclic antidepressant. Use of duloxetine (60 mg daily) is supported by level 1 evidence in patients with diabetic peripheral neuropathic pain. In many cases it is a safer alternative than

COMMON SIDE EFFECTS OF FIRST-LINE ORAL DRUGS FOR NEUROPATHIC PAIN

Tricyclic antidepressants
- Drowsiness
- Confusion
- Dry mouth
- Orthostatic hypotension
- Weight gain
- Urinary retention
- Cardiac arrhythmia

Serotonin and noradrenaline reuptake inhibitors
- Nausea
- Dry mouth
- Drowsiness
- Sexual dysfunction

Alpha-2-delta ligands
- Dizziness
- Drowsiness
- Peripheral oedema
- Weight gain

a tricyclic antidepressant, especially where depression is significant and a full antidepressant dose is required. There is evidence of efficacy for venlafaxine at higher doses (150 to 225 mg daily), at which levels noradrenaline reuptake inhibitor activity becomes apparent.

The selective serotonin reuptake inhibitors have much less evidence of effectiveness in neuropathic pain than the tricyclic antidepressants or SNRIs.

Alpha-2-delta ligands

The anticonvulsants gabapentin and pregabalin have both been studied widely in patients with neuropathic pain and, along with tricyclic antidepressants, represent first-line options for the treatment of this type of pain. They are believed to act through binding to the alpha-2-delta subunits of calcium channels in the central nervous system, reducing the influx of calcium into neurons and in turn decreasing neurotransmitter release.

Gabapentin and pregabalin are relatively safe alternatives to antidepressants, with their main side effects being dose-related drowsiness or dizziness and, less frequently, peripheral oedema and weight gain. As with tricyclic antidepressants, careful titration of these sedating drugs can improve sleep without causing daytime drowsiness. These agents have generally been demonstrated to be anxiolytic but not antidepressant in study groups with neuropathic pain.

Other anticonvulsants

Carbamazepine remains the first-line treatment for the relatively rare condition of trigeminal neuralgia but is not generally used for other forms of neuropathic pain. The evidence is equivocal for its efficacy in the more common forms of neuropathic pain, and patients require careful blood monitoring for the development of blood dyscrasias and hepatotoxicity. The evidence is likewise mixed for the efficacy of sodium valproate in neuropathic pain. Lamotrigine is occasionally used for neuropathic pain and this is supported by some trial evidence; its major adverse effects are serious dermatological conditions such as Stevens–Johnson syndrome.

Opioids

Traditionally, neuropathic pain has been considered resistant to treatment with opioids. In fact, randomised controlled trials show that the number needed to treat (NNT) with opioids in neuropathic pain is quite similar to the NNT with tricyclic antidepressants and also to the NNT with opioids in trials on nociceptive pain. In spite of this, with the exception of some forms of acute neuropathic pain and cancer pain, opioids are generally recommended as third-line agents because of the frequency of adverse effects and uncertainty about their long-term efficacy.[4,5]

There is trial evidence supporting the use of tramadol, which is both an SNRI and a weak mu opioid receptor agonist, in a number of neuropathic pain states. It may be recommended as a second- or third-line treatment for patients who are not taking, and are not likely to later require, an antidepressant as part of pain management.

Topical treatments

Lignocaine transdermal patches have level 1 evidence of effectiveness in relatively localised forms of neuropathic pain such as postherpetic neuralgia. Capsaicin cream has limited evidence of effectiveness and is not commonly tolerated in the longer term.

Combination therapies

With the recommended treatments requiring an average of three people to be treated to reduce one patient's pain by 50%, it is clear that many patients will require serial trials or a combination trial of proven medications. Theoretically, combining drugs with different mechanisms of action and different adverse effects has the potential to provide better pain relief with fewer side effects. Results of recent trials have been promising, with combinations of antidepressants, alpha-2-delta ligands and opioids reducing both side effects and NNTs.[6]

NONPHARMACOLOGICAL APPROACHES

When the response to proven medications is not satisfactory then adopting a broader rehabilitation approach is likely to be preferable to trials of high doses or combinations of unproven medications. Few randomised controlled trials have assessed nonpharmacological approaches to neuropathic pain, in contrast to osteoarthritic and nonspecific low back pain.

Cognitive behavioural therapies and especially pain management groups have excellent face validity, and should be considered whenever psychosocial comorbidities are significant or when responses to pharmacological approaches are unsatisfactory. Australian physiotherapists have

been at the forefront of research on the use of guided motor imagery, including mirror box therapy, with NNTs in complex regional pain syndrome being similar to the NNTs with the far more expensive and invasive option of spinal cord stimulation.

SUMMARY

- Research into treatments for neuropathic pain has expanded rapidly in the past decade, and there is growing consensus about its management.
- Management should include education of patients and their families about neuropathic pain and how it differs from nociceptive pain.
- Selection of first-line medications for treatment of neuropathic pain should take into account the presence and severity of the common comorbidities of sleep disturbance, depression and anxiety, and also, particularly in the elderly, medical comorbidities.
- Tricyclic antidepressants, SNRI antidepressants (duloxetine and venlafaxine) and alpha-2-delta ligands (gabapentin and pregabalin) are first-line choices for most types of neuropathic pain, with tramadol and opioids being second- or third-line options. Topical lignocaine patches are a first-line choice for localised neuropathic pain.
- If single agents are not sufficiently effective or cause intolerable side effects at high doses then judicious combination therapy using drugs with different mechanisms of action and largely different side effects may be an appropriate therapeutic alternative.
- If the response to proven medications is unsatisfactory then adopting a broader rehabilitation approach is preferable to trials of high doses or combinations of unproven medications. MT

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