Neuropathic pain

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John Barnard *is an Anaesthetist/Pain Specialist at Waikato Hospital. He has worked in the field of pain medicine for the last 14 years, the last six at Waikato Hospital. He has a broad practice within this speciality. Liaison with GPs is an enjoyable and important part of his job. As with any chronic disease, the bulk of the medical input for neuropathic pain is provided by doctors in Primary Health care.*

To be useful in a clinical sense any classification of pain must lead to some meaningful change in the way in which pain is diagnosed, treated, or managed. Neuropathic pain is commonly used in pain classification. How is it useful then, to consider that the origin of pain is within the nervous system, rather than being at the site of actual or potential tissue damage, in a particular patient?

Diagnosis

This classification encourages us to look beyond tissue damage and inflammation, to find evidence of damage to the nervous system with specific history taking, and clinical examination. Generally investigations are used to confirm rather than make a diagnosis, or to provide clear anatomical information prior to surgery. Burning pain, tingling or prickling dysaesthesia, and lancinating or electric shock pain are all indicators that the pain could be neuropathic. Likewise, on examination, pain in an area of altered sensory and/or motor function is an indicator.

While few elements of the history are pathognomic for neuropathic pain,[1,2] often the picture painted is unusual in some way. This is not simply because the pain is out of proportion to any visible tissue injury, but the descriptions are often quite bizarre with respect to:

- *the intensity of pain* – 'molten lead'
- *sensory distortion* – cold feels warm, light brush is painful
- *perception of anatomical distortion* – 'my toe is bent under my foot', 'my foot is swollen'(when it isn't)
- *unpredictability* – 'any time of day or night'

Phantom limb pain and post herpetic neuralgia are two of the most straightforward neuropathic pain diagnoses, but even in these two examples it is possible that there are important nociceptive components making the neuropathic pain more florid, e.g. ischaemia or infection in a BKA stump. The converse, a pain being mistakenly diagnosed as nociceptive, and the neuropathic element ignored, is a more common clinical scenario, e.g. wound pain after surgery secondary to nerve injury. Unfortunately the picture is often mixed and may become clear only with time and failed interventions.

A number of screening instruments have been developed to aid in the diagnosis of neuropathic pain. Pfizer have piggy-backed a useful and short screening questionnaire (DN4) onto their recent promotional material for the prescribing of gabapentin for neuropathic pain. The DN4 was developed by Bouhassira and co-workers.[3]

Drug treatment

Therapeutic drug treatment options can be divided into those that are disease specific (few) and those that are widely applicable (most). Recent reviews for the diagnosis and treatment of ZAP/PHN (Zoster associated pain/post-herpetic neuralgia), PDN (painful diabetic neuropathy), and trigeminal neuralgia,[4,5,6] have been published. These reviews are weighted towards pharmacological treatment with the latest agents. Some of the drugs suggested are either not available in New Zealand or not affordable by the average patient. Another potential problem is simply the number of different medicines and therefore the near countless combinations. The positive thinker would point out at this stage that no matter how many times a patient presents to your clinic there will always be another pharmaceutical cocktail to try. Clearly though, there is danger in this approach, the most obvious of which is the virtual absence of good information about combinations of adjuvant analgesics with respect to any synergy of effect and of side effects. Once you have read a few of the review articles it soon becomes clear that the spectrum of drugs used for each neuropathic pain is very similar. Add to this the restricted range of medicines available in New Zealand and you end up with a more reasonable list of medications and therefore numbers of combinations to try.

The academic medical community is heavily dependent on the pharmaceutical industry's financial support for large randomised controlled trials. It comes as no surprise then, that the focus of the research generated is

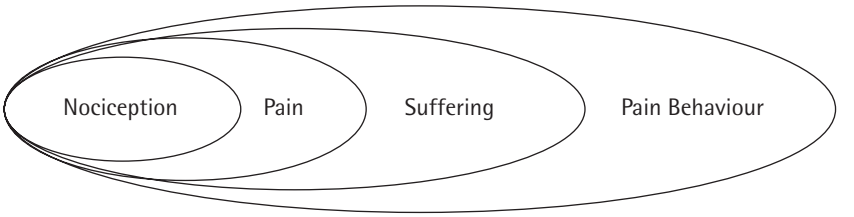
to demonstrate effectiveness of new therapies over placebo, with the additional aim from the same trials of demonstrating better safety profiles than alternative older drugs. Head to head comparisons of gabapentin with carbamazepine, sodium valproate or clonazepam are relatively rare. While these trials do demonstrate the superior tolerability of gabapentin, in general, this newer drug has not been found to be any more effective. Overall the tricyclic antidepressants remain the most reliably effective agents.

The last decade or two has witnessed an unprecedented volume of basic science research into the mechanisms of neuropathic pain.[7] There have been many important discoveries, e.g. the nature of the painful heat receptor, the central role of the NMDA receptor in hyperalgesia, the demonstration of cortical reorganisation on fMRI. However, the overall impact on the drug treatment of neuropathic pain has been relatively unimpressive. The adjuvant analgesics, with few exceptions, have to be tried in an empiric fashion rather than given on the basis of a specific neuropathic pain symptom or disease and no one has managed to find a 'safe' opioid. There is a degree of optimism that this situation will change.[8] Evidence-based medicine (EBM) tells us that tricyclic antidepressants have an NNT (number needed to treat) of 2.7 when given for post herpetic neuralgia, i.e. on average we will need to treat almost three patients to find one that has a successful response (threshold of success usually set at a 50% reduction in their pain). It cannot tell us whether a specific patient will get a greater benefit than harm from this class of drugs, nor whether that patient will find the benefit worthwhile.

Management

There is an important difference between treating and managing. The latter implies an active, thoughtful participation by the patient. With neuropathic pain, as with many chronic conditions, it is a better concept than treatment. Drug therapy for pain is often a component of a management plan, but there may well be other important therapeutic targets for the drugs such as mood, sleep, appetite, concentration, muscle tension etc., and also other modes of therapy. The range of therapies spans the gamut from psychological to spiritual to physical.

Figure 1. Loeser's model of pain



In many ways calling pain pathological is more useful than calling it neuropathic. If, however, defining pain as a disease state in its own right is a bridge too far, then try the definition complex pain. While it is reasonable to remain open to the chance that there is reversible or treatable pathology, greater gains for the patient may be made through careful consideration of why the patient is presenting to your surgery. Loeser's model of pain is a good starting point (Figure 1). It emphasises the fact that we can only be aware of the patient's pain through their pain behaviour, which may be voluntary or involuntary. Nociception is the process of detecting tissue injury and conveying this sensory information to the central nervous system.

The same model can be presented as a bar chart (Figure 2). It is a gross simplification, e.g. not all acute pain responds so well to morphine. With complex pain the level of pain behaviour is less closely related to the level of nociception. This implies that even if the nociceptive input is reduced the pain behaviour you see may remain high.

The step up taken to get to the top of the first bar then each subsequent step demand attention. Each represents a target for management. Imagine a patient presenting with marked pain behaviour and describing their pain as excruciating. If the biggest steps are towards the left (nociception and pain) then it is likely that surgical or medical therapy alone will make a significant difference and that opioids, despite their strongly reinforcing nature and their adverse cognitive effects, could have an important role. In contrast, if the biggest steps are towards the right then it is likely that medical and cognitive-behavioural therapy hold the most promise, and that the use of opioids is unlikely to be of net benefit.

Complex (or pathological) pain avoids the technicalities of trying to decide whether the pain of chronic low back pain or complex regional pain syndrome is the result of nerve injury or the result of a process of central nervous system reorganisation/plasticity/sensitisation. The same framework is equally valid for visceral pain. It encourages consideration of the cognitive and social components of a pain presentation. Brief notes on two types of complex pain follow, the first relatively straightforward and usually neuropathic, the second a morass of diagnoses and dilemmas.

Post amputation pain

This includes two pains (stump and phantom pain) and a non-painful sensation (phantom limb sensation). The most common setting is post amputation of a limb or arm or part thereof, but basically anything being chopped off may result in troublesome pain.

'Ordinary' stump pain is felt immediately post amputation, secondary to nociception at the site of injury (surgery). Generally it settles

over a few days and is managed in a similar way to other post-operative pain. There are two reasons why stump pain may persist. Firstly there may be ongoing nociception in the stump, e.g. infection, ischaemia, inflammation etc., secondly the stump pain may be secondary to nerve injury in a similar way to phantom pain (see below).

Phantom limb sensation is simply feeling like the amputated part is still attached. Virtually everyone will get this. It may be incredibly real to the person, complete with phantom movements. Phantom sensations will distress some people, but just because a particular patient is distressed and they find the sensations unpleasant (dysaesthesia) doesn't mean the sensations are painful. Phantom sensations are not readily treatable with medication but do tend to fade with time. Interestingly the phantom limb tends to telescope into the stump, e.g. a phantom leg gets shorter and shorter until finally the foot disappears into the stump.

Phantom limb pain is simply pain felt in the amputated part, e.g. pain in the left foot after left BKA. It is the ultimate example of a neuropathic pain, i.e. a pain that is generated within the pain pathways rather than by a nociceptor being stimulated. Most patients will have some phantom pain, but severe intrusive pain is relatively uncommon (approx 10%). Typically the pain is well localised and described as either continuous burning or shooting 'electric'. However, the nature of the pain varies widely (anything is possible). Adjuvant analgesics are widely used (antidepressants, anticonvulsants, membrane stabilisers etc.). The treatment of chronic phantom limb pain remains imperfect and a wide range of techniques both pharmacological and non-pharmacological may be helpful (from psychotherapy to dorsal column stimulation).

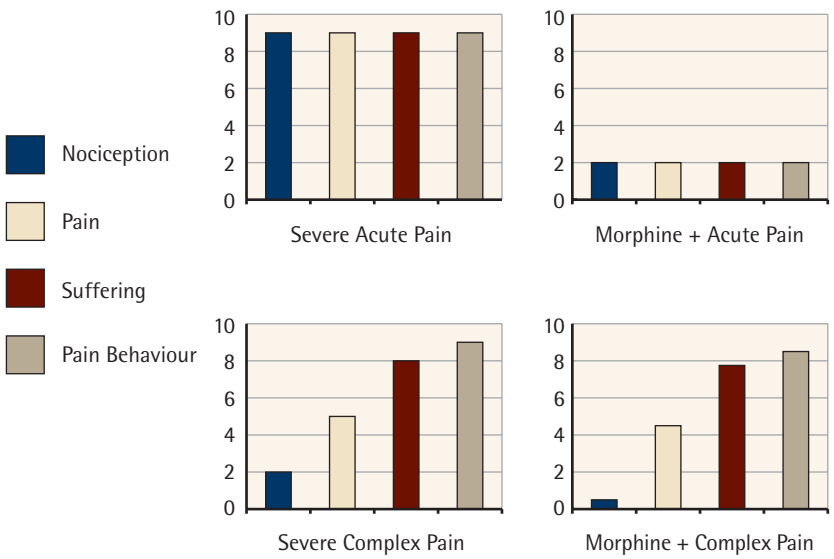
Two popular preventative options are regional analgesia peri-operatively and calcitonin infusions when phantom pain starts.

Low back and leg pain (LBP)

Adult back pain research provides much of the data on the impact of pain on society. In the words of Gordon Waddell (Orthopaedic Surgeon) *'Back pain is a twentieth century health care disaster.'*[9] The majority of people (70–85%) will have back pain at some time in their lives, the point prevalence is somewhere around 20%. Most people do not become chronic suffers. Eighty-five per cent of people with back pain return to work within six weeks, however 40% still report considerable pain and dysfunction at one year. Although only a small number of people become chronic sufferers, this small percentage, probably around 6%, consume over 50% of the health care costs related to back pain. A New Zealand study showed that the average back pain patient visited their doctor 12.9 times per year. The cost to society is huge. Two per cent of the US workforce are compensated for back pain each year and back pain is estimated to cost that country $70 billion in 1983. In the UK it is the largest single cause of absenteeism from work. In Sweden 15% of all sick leave is due to back pain. The increase in back pain over the last 50 years has been incredible; in the UK the number of work days lost due to back pain was 5000 in 1953 and 45 000 in 1990. In the US the number of new social security payments per year for back pain increased by 2680% between 1953 and 1975. Despite the massive increase in compensation, the prevalence of back pain is thought to have changed little.

Back and leg pain also highlights the difficulty of diagnosing pain when there are multiple potential causes of pain. Sciatica is a commonly used term that strictly should be used only when there is radicular leg pain in the distribution of the sciatic nerve caused by injury to the sciatic nerve or its nerve roots. There should be other signs of nerve dysfunction to accompany the pain, like altered sensation in the relevant dermatomes, reduced ankle jerk, decreased strength of plantar flexion. Commonly the term is used much less specifically incorporating all leg pain associated with a sore back. At each lumbar spinal segment the following structures can cause leg pain: the intervertebral discs, the facet joints, the posterior longitudinal ligaments, the inter- and supra-spinal ligaments, the paraspinal musculature and more. More confusion is added by sensitivity of MRI and CT scanning. For example about 30% of asymptomatic 40 year olds will have a significant abnormality on their lumbar spine

Figure 2. The response to morphine of acute and complex pain



MRI. How then do you identify the lesions that are causing pain and which should be operated on? Further evidence about the difficulties of managing back and leg pain is the plethora of alternative therapies available to the sufferer. Many of these seem to provide a worthwhile therapeutic effect to a proportion of those with back pain and leg pain but most have not been studied with any degree of scientific rigour.

In the pain clinic we often see the extreme end of the spectrum of chronic back pain, in terms of chronicity, intensity, and secondary distress and disablement. We take a relatively conservative approach, chiefly utilising education (about many aspects of chronic pain), activation (a stronger patient will be less disabled and more confident in moving), relaxation (a learnt ability to recognise and reduce tension, not just sitting in front of the rugby etc.), sensible use of oral analgesics, and very occasional use of invasive and interventional techniques such as dorsal column stimulation, and epidural and intrathecal drug administration.

So what and how should a GP prescribe – in 500 words or less?

The first choice agents remain tricyclic antidepressants despite reluctance on the part of the patient to take a tablet used to treat depression when the presenting problem is pain and, equally, despite concerted efforts by the pharmacological industry to get us to use products still under patent. Second line drugs include anticonvulsants and clonidine. There are a variety of other drugs that could be considered but probably by the time you have run adequate trials of the first and second line drugs referral to the nearest pain clinic would be worthwhile.

Tricyclic antidepressants (TCAs) as a class of drugs share more than structural features.[10,11] They act on a similar spectrum of receptors. However, the potency at each receptor subclass varies quite markedly between agents. They can be ranked by their activity at three of their sites of action and their side effect profiles reflect this ranking. I have ranked the agents I use most below. Amitriptyline (A); Nortriptyline (N); Imipramine (I); Doxepin (D). In the elderly I start with nortriptyline. In the younger age group I start with amitriptyline. Imipraine may be useful when sedation is a particular concern but postural hypotension is a significant risk.

- Anti-cholinergic (dry mouth, blurry vision urinary retention, confusion) A=D>N>I
- Antihistamine (sedation) A=D>N>I
- Alpha adrenergic blockade (postural hypotension) I>A=D>N

All of the agents cause prolongation of QT interval and their plasma levels will be increased by fluoxetine through pharmacokinetic interaction. Exactly what receptor(s) need to be affected to relieve pain is unknown but selective serotonin reuptake inhibitors (SSRIs) are not considered to be as effective as analgesics as TCAs. Start with low doses, 10mg nocte (even 5mg in the elderly). Titrate dose upwards by about 10–25mg each week. There is some disagreement in the literature about what dose constitutes a reasonable trial given that dose is not limited by side effects. In my own practice I seldom go above 100mg and in the presence of significant doses of tramadol or SSRIs will not go above 50mg. I have a low threshold for combining TCAs with second line drugs.

Anticonvulsants as second line drugs are not particularly benign medicines.[8] Carbamazepine, sodium valproate, and clonazepam are all reasonable choices. However, in general, once I have tried one of these I will apply for gabapentin funding on the basis that it is a safer drug. The basis of my choice of which of the older agents to use and starting doses (in brackets) follows. Carbamazepine is the best studied of the older anticonvulsants (100mg nocte or BD) and probably the most effective, valproate has some mood stabilising effects and probably augments antidepressants (200mg nocte) and clonazepam has the best anxiolytic properties (0.25mg nocte). Each drug, however, has significant down sides. Carbamazepine causes ataxia and fatigue, valproate deranged LFTs and tremor, and clonazepam sedation and its use is likely to result in some tolerance and dependence formation. Gabapentin has a better side effect profile. A dosing schedule for gabapentin is available from the author on request.

Clonidine, either as a patch or as tablets has a number of useful features. It is analgesic in its own right, it augments opioids, reduces sympathetic outflow, and can aid sleep. Postural hypotension, sedation, hypertension on withdrawal and dry mouth can all be dose limiting side effects. The patch can leave a rash. Starting dose 50–100mcg/24hr as daily or BD tablets, or as patch (can cut the patch in half).

Others include baclofen, lamotrigine, newer antipsychotics, methylphenidate, anti-oxidants, B group vitamins, botulinum toxin etc. When the situation allows, consider topically active preparations such as local anaesthetics, capsaicin, NSAID, chloroform and aspirin.

Keep in mind that you can learn at least as much about drug effectiveness on stopping a drug as starting a drug. Also that measuring success by change in function, either for the better or the worse, is at least as important as measuring change in the simple domain of pain intensity.[12]

How can a cognitive behavioural approach be used in general practice?

Cognitive behavioural therapy can be achieved in a low intensity way, in 'sound-bites'. The following is a list of important concepts.

- Weak link between hurt and harm
- Strong link between inactivity and disablement
- Personality traits become more obvious with the stressor of chronic pain
- Illness belief/sick role reinforced by medicalisation

- Fear and catastrophising strongly reinforced by pain
- Pacing preferable to boom/busting
- 'Stress', lowered mood and poor sleep do not give you chronic pain but they can make it worse and always make it much more difficult to cope with
- The patient's environment, and relationships, may be maladaptive
- Similar to asthma, or diabetes or pretty much any other significant chronic disease, chronic pain requires a management approach
- The chronic pain is just as real as acute pain though the link with a physical arousal/stress response is often absent, i.e. no raised BP or sweating, yet the emotional response to the pain is dramatic.

Commonly, complete relief from neuropathic pain is often unrealistic and the continued search for a pain cure by drug or knife becomes positively harmful. The search is harmful through the confirmation of illness belief, the cycle of hope and recurrent treatment failure, the emphasis on an external locus of control, and the direct adverse effects of the specific treatment regime.[13] Some of the greatest improvements in quality of life I have seen have been when the patient makes a transition from fighting/ignoring/beating their pain to accepting/living with/working with their pain.

Recommended websites

College of Anaesthesia, Acute Pain Management: Scientific Evidence
www.anzca.edu.au/publications/acutepain.pdf

ACC, has an excellent range of provider information e.g. Interventional Pain Management, Tramadol for chronic pain, Acute low back pain guidelines
www.acc.co.nz

Waddell's back pain book available online at mdconsult
Home.mdconsult.com/da/book/61597745-2/view/1221

When to refer to the pain clinic?

In theory at least, the pain clinic is not the clinic you refer to because nobody else is willing to offer specialist assessment. The converse should be closer to the truth. In general we would expect a patient to be seen by an organ specific specialist prior to referral to our clinic. For instance, a neurologist or a general physician should normally assess a patient with severe headache before referral to the pain clinic takes place. Severe pain in and of itself is not sufficient reason for referral. There should be a clear expectation that either yourself, as the referrer and/or your patient is likely to benefit from the pain clinic assessment taking place. Waiting list times will vary markedly.

Pain clinics can generally offer:

- A coordinated multidisciplinary assessment spanning the physical to the psychological, the major aims of which are to:
  - Understand the patients pain in the context of the whole person
  - Determine whether further diagnostic tests are needed
  - Document the current impact of pain on the sufferer
  - Identify targets for therapy
  - Advocate for the patient within the hospital outpatient system
- A range of therapies – psychological, social, drugs, injection techniques etc.
- Support for GPs when trying to set boundaries for difficult patients.

Competing Interests

None declared.

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