Neuropathic pain in advanced cancer: causes and management

Pain can affect up to 75% of patients with advanced cancer and it is estimated that 30-40% of cancer pains have a neuropathic element (Roberto et al, 2016; Bennett et al, 2012). A person with advanced cancer may experience neuropathic pain as a consequence of the cancer itself, anti-cancer treatment or a co-existing condition (Bennett et al, 2012). Neuropathic pain – the physiology of which is outlined in Box 1 – is thought to be more detrimental to physical and psychological wellbeing than nociceptive pain (Ulas et al, 2018; Oosterling et al, 2016). It can adversely affect mood, sleep, social interaction and independence; its presence in cancer may delay treatment, limit treatment options or lead a patient to refuse treatment (Esin and Yalcin, 2014; Lema et al, 2010).

Managing neuropathic pain in cancer often requires use of adjuvant analgesics alongside more traditional analgesia. If medications fail to control the pain, it may be necessary to consider interventional procedures. Nurses are well placed to assess pain severity and impact on quality of life, as well as monitoring treatment responses and ensuring patients receive the right support.
Neuropathic pain. The same study estimated that 40% of cancer pains have a neuropathic element. The same study estimated that 60% of cancer pain is nociceptive, with neuropathic pain and mixed pain each accounting for another 20%; this suggested that 40% of cancer pains have a neuropathic element. The same study estimated that neuropathic pain in cancer may remain problematic long after completion of the chemotherapy regimen (Farquhar-Smith, 2011). Depending on the agent used, its dose and treatment duration influence neuropathic pain related to chemotherapy. There may also be a cumulative effect and patients with pre-existing nerve damage are more at risk (Farquhar-Smith, 2011). Depending on the agent used, chemotherapy-induced neuropathic pain may occur hours, days, weeks or months after administration, and may remain problematic long after completion of the chemotherapy regimen (Farquhar-Smith, 2011). Neuropathic pain associated with chemotherapy often affects the distal part of limbs – this is known as 'stocking and glove' distribution.

Clinical features
The presentation of neuropathic pain varies. The temporal pattern may be:
- Constant;
- Intermittent;
- A constant background pain with intermittent bursts of severe pain;
- Spontaneous bursts of pain;
- Pain occurring only when evoked (Fallon, 2013; Finnerup and Jensen, 2015).

Neuropathic pain is commonly described with terms such as 'burning', 'shooting', 'tingling' or 'electric-shock-like'; there may also be areas of reduced sensation or numbness. Although such descriptors are highly suggestive of neuropathic pain, they are not diagnostic (Finnerup and Jensen, 2015). Areas of sensory abnormality often accompany neuropathic pain (Table 3). The distribution of the pain follows the tract of the nerve(s) affected, but both pain and sensory abnormality may extend beyond the expected distribution of the nerve (Gilron et al, 2006). It may also persist after the pain-inducing stimulus has been removed.

Assessment
As neuropathic pain can significantly lower a mood and interfere with the ability to work or take part in social and leisure activities, its impact cannot be gauged by the severity of the pain alone. Nurses are well placed to help assess the pain’s multidimensional effects on the patient. Pain assessment needs to be comprehensive, with each individual pain examined separately, at its best and worst. Recording words used by the patient to describe the pain and its impact is valuable. Assessment should include:
- Description of the pain type (burning, shooting, aching, electric, etc);
- Pain severity, in words (for example, mild, moderate, severe), numerical value or using a visual analogue scale;
- Temporal features (for example, constant, intermittent, constant background pain with exacerbations);
- Pain location (use a body chart to help record location and distribution);
- Exacerbating and relieving factors;
- Whether it is spontaneous or evoked;
- Pain history (for example, how long it has been present, changes over time);
- Effects of current and previous interventions, including analgesics used;
- Effect of pain on sleep;
- Underlying disease process and presence of comorbidities;
- Psychological impact (including what the pain means to the patient);
- Social impact.

Box 1. Physiology of neuropathic pain: an overview

The physiology of neuropathic pain is complex and only partly understood. A detailed analysis of the multiple mechanisms identified so far is beyond the scope of this article, but this brief overview helps show how adjuvant analgesics may provide pain relief.

Damage to peripheral nerves results in changes at cellular and molecular levels that cause sensitisation of the peripheral and central nerve pathways (Gilron et al, 2015). This can cause painful stimuli to be amplified and prolonged, non-painful stimuli to be interpreted as pain and spontaneous bursts of pain to occur without prior stimulus; the overall effect is an increased sensation of pain (Gordon-Williams and Dickenson, 2015). Factors leading to peripheral sensitisation include:
- Release of a range of chemical mediators that promote the transmission of painful stimuli (Gordon-Williams and Dickenson, 2010);
- Proliferation of sodium channels and calcium channels leading to increased excitability of nerve fibres and ectopic discharges (resulting in spontaneous pain) (Finnerup and Jensen, 2015);
- The increased activity of the peripheral nervous system results in central sensitisation by a range of mechanisms:
  - Activation of N-methyl-D-aspartate receptors, which result in an increased perception of pain (Finnerup and Jensen, 2015; Gordon-Williams and Dickenson, 2010);
  - Nerve fibres that are normally associated with the sensation of touch gain access to pain pathways. Consequently, what would normally be considered a non-painful stimulus is perceived as painful (Finnerup and Jensen, 2015);
  - Reduced inhibitory regulation of pain (Gilron et al, 2015; Connolly et al, 2012);
  - Activation of microglia – specialised cells in the central nervous system that are involved in immune response – in the spinal cord, causing the release of various substances that enhance pain transmission (Gilron et al, 2006).
- Sensitisation by a range of mechanisms:
  - Activation of N-methyl-D-aspartate receptors, which enhance pain transmission (Gilron et al, 2006).

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Table 1. Pathophysiology of cancer pain

<table>
<thead>
<tr>
<th>Pain type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Nociceptive</td>
<td>Pain arising from actual or threatened damage to non-neural tissue due to the activation of nociceptors and occurring within a normally functioning somatosensory nervous system. Further classified as:</td>
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<tr>
<td></td>
<td>- Somatic pain: relating to damage of structures such as bone and muscle</td>
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<td></td>
<td>- Visceral pain: relating to a lesion in, or compression of, a hollow viscus or solid organ</td>
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<tr>
<td>Neuropathic</td>
<td>Pain caused by a lesion or disease of the somatosensory system that is a consequence of a malfunctioning nervous system</td>
</tr>
<tr>
<td>Mixed</td>
<td>Both a nociceptive and neuropathic component</td>
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</table>

Sources: Yoon and Oh (2018), Esin and Yalcin (2014), International Association for the Study of Pain (Bit.ly/PainTerminology)
Assessment will also require neurological examination, including response to touch, pinprick, vibration and heat, along with mapping areas of dysfunction (Gilron et al, 2015; Connolly et al, 2012). Jones and Backonja (2013) and Eckeli et al (2016) have provided useful overviews on a range of assessment tools to help identify neuropathic pain or pain with a neuropathic component; these include the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Questionnaire, Douleur Neuropathique 4 (DN4), ID Pain and the Standardised Evaluation of Pain (STEP).

All seek to identify the presence of common features suggestive of neuropathic pain (for example, ‘burning’, ‘pins and needles’, ‘electric shocks’), although the range of potential signs in each varies. Some tools are designed for self-administration by the patient; others are completed by a health professional. Physical assessment is included in some tools – such as LANSS, DN4, STEP – to ascertain whether sensations such as allodynia, hyperalgesia or dysaesthesia can be evoked. Sensory abnormalities are summarised in Table 3.

The Neuropathic Pain Scale is for use in patients already diagnosed with neuropathic pain (Jones and Backonja, 2013), and can be useful when monitoring treatment responses. Symptom severity is rated 0–10.

To monitor a response to interventions, assessment must be ongoing. The appropriate 0–10.

Management
The impact of neuropathic pain is multidimensional. Management needs to be individualised and is best delivered though a multidisciplinary team approach (Gilron et al, 2015). Nurses can help give patients adequate explanations about treatments, the opportunity to raise concerns and time to answer their questions. This can reduce patients’ feelings of uncertainty and promote concordance with treatment.

Psychological and behavioural interventions can also help patients optimise their own coping strategies (Cassileth and Keefe, 2010). These can include providing:

- Patient education on how psychological factors (thoughts, feelings, behaviours) can influence and be influenced by pain;
- Training in pain-coping skills that are cognitive (such as imagery and distraction strategies) or behavioural (such as activity pacing and relaxation).

Pain and sensory abnormalities may impair patients’ ability to perform daily activities or reduce their independence in other ways (Oosterling et al, 2016). If lower limbs are affected by pain or abnormal sensation, the risk of falls increases. There may also be financial concerns if the patient’s ability to work is reduced or a relative is struggling to find employment due to caring responsibilities.

Nurses can be the first to identify such issues, prompting referral to physiotherapists, occupational therapists, social workers and benefits advisers, as appropriate. Complementary therapies such as massage, acupuncture or transcutaneous electrical nerve stimulation (also known as TENS) may be helpful for some patients, although evidence of their overall benefit is not well established (Esin and Yalcin, 2014; Fallon, 2013; Pittler and Ernst, 2008).

Treating the underlying cause of neuropathic pain is advocated but, often, this is not possible – with pain relating to advanced cancer a more symptomatic approach may be required.

Pharmacological treatment
A pharmacological approach is the mainstay of managing neuropathic pain in patients with cancer, although there are challenges. These include:

- Analgesic response is variable;
- Pain reduction is often partial;
- Neuropathic pain often co-exists with other pains or the pain has a nociceptive element;
- Combination therapy is often required, resulting in multiple medication regimens and the risk of additive toxicity (Esin and Yalcin, 2014; Fallon, 2013; Finnerup and Jensen, 2015).

<table>
<thead>
<tr>
<th>Potential cause</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Disease</td>
<td>Painless</td>
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<tr>
<td>Treatment</td>
<td>Surgical</td>
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<tr>
<td>Co-existing condition</td>
<td>Diabetes</td>
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Sources: Esin and Yalcin (2014), Fallon (2013)

<table>
<thead>
<tr>
<th>Sensory abnormality</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>After-sensation</td>
<td>Pain outlasts duration of stimulus</td>
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<tr>
<td>Allodynia</td>
<td>Pain triggered by non-painful stimulus; for example, gentle touch, moderate cold or warmth</td>
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<tr>
<td>Dysaesthesia</td>
<td>Unpleasant abnormal sensation (spontaneous or otherwise)</td>
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<tr>
<td>Enhanced temporal summation</td>
<td>Escalating pain in response to repeated application of constant stimulus</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>Increased sensation of pain from normally painful stimulus</td>
</tr>
<tr>
<td>Hypoalgesia</td>
<td>Diminished sensation of pain from normally painful stimulus</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>Abnormal sensation (spontaneous or evoked)</td>
</tr>
<tr>
<td>Secondary hyperalgesia</td>
<td>Pain and hypersensitivity beyond dermatome of nerve injury</td>
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</tbody>
</table>

Sources: Fallon (2013), Finnerup and Jensen (2015); Gilron et al (2015), International Association for the Study of Pain (Bit.ly/PainTerminology)
Medication regimens can be complex and input may be needed from specialist pain or palliative care teams to oversee management. Several medications used to manage neuropathic cancer pain were developed for other indications (for example, depression and epilepsy) and their benefits in treating neuropathic pain were established in non-malignant conditions (such as post-herpetic neuralgia and diabetic peripheral neuropathy) (Gilron et al, 2015). These are often called ‘adjuvant analgesics’, although they are increasingly considered primary analgesia for selected pain disorders (Twycross et al, 2017; Lussier and Portenoy, 2015). First-line adjuvants are outlined in Table 4.

To minimise the risks of side-effects, adjuvant analgesics should be introduced gradually, then slowly increased over time, while their effect is closely monitored (Lussier and Portenoy, 2015). It can take several weeks at therapeutic levels before an analgesic effect is noted; this needs to be explained to the patient carefully to help promote concordance. The National Institute for Health and Care Excellence (2018) advises considering the following when choosing an adjuvant:
- Contraindications and potential adverse effects;
- Interactions with other medications;
- Comorbid conditions that may benefit from specific treatment (for example, people with depression may benefit from an antidepressant drug);
- Patient preference.

There is little evidence that the pain description should guide the choice of adjuvant, such as an anticonvulsant for burning pain or an antidepressant for shooting pain (Finnerup and Jensen, 2015). Adjuvant medications, which act by different mechanisms, can be used in combination when a single adjuvant gives insufficient relief (Twycross et al, 2017). While combination therapy is often required to manage neuropathic pain, evidence is insufficient to recommend specific combinations or dose ratios (Chaparro et al, 2012).

Although opioids are not considered first-line agents for neuropathic pain that is either associated with non-malignant conditions or purely treatment-related, they are considered first-line agents for neuropathic pain caused directly by the cancer (Twycross et al, 2017; Connolly et al, 2012). The reasons for this are:
- In patients with cancer, instead of existing in isolation, neuropathic pain may exist with another pain that is highly opioid-responsive;
- Some patients will achieve a better analgesic effect or reduced side-effects with an opioid compared with an adjuvant (Fallon, 2013).

Unless a pain is likely to respond to a specific adjuvant, opioid therapy should be optimised before an adjuvant analgesic is introduced. This reduces the risk of additive toxicity – when two or more medications have similar side-effects, the side-effect may become more severe if those medications are taken together (Lussier and Portenoy, 2015). Concurrent use of an opioid and an adjuvant can give more effective relief at lower doses than using the drugs singly at larger doses, but patients need to be monitored for signs of adverse effects (Esin and Yalcın, 2014; Connolly et al, 2012).

**Antidepressants**

The analgesic effect of antidepressants is independent of their antidepressant effect (Gilron et al, 2015; Fallon, 2013; Lussier and Portenoy, 2010) so the dose required to achieve an analgesic effect is often lower than that required to achieve an antidepressant effect (Finnerup and Jensen, 2015). Amitriptyline (a tricyclic antidepressant) and duloxetine (a selective serotonin norepinephrine reuptake inhibitor) are seen as first-line treatments for neuropathic pain (NICE, 2018). Other antidepressants used to treat neuropathic pain, but with less-supportive evidence for their use, include imipramine, nortriptyline and venlafaxine.

An antidepressant may be the first choice of adjuvant for patients with neuropathic pain who also have depression.

**Anticonvulsants**

An increased understanding of the importance of hyperexcitability as a mechanism in the physiology of neuropathic pain has promoted the use of anticonvulsant drugs – and particularly gabapentinoids – to manage it (Esin and Yalcın, 2010). Gabapentin and pregabalin are both considered.

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**Table 4: First-line adjuvants to treat neuropathic pain**

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Mode of action</th>
<th>Potential side-effects</th>
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<tbody>
<tr>
<td><strong>Antidepressant</strong></td>
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<tr>
<td>Tricyclic antidepressant (for example, amitriptyline)</td>
<td>- Blocks reuptake of norepinephrine and serotonin to enhance inhibitory pain pathways descending from brain stem - Blocks voltage-gated sodium channels - Central NMDA receptor antagonist</td>
<td>- Dry mouth, constipation, urinary retention, blurred vision - Older people at increased risk of somnolence, hypotension and gait disturbance - Contraindicated for patients with epilepsy, heart failure and conduction blocks - Avoid concurrent use of tramadol (risk of serotonin syndrome)</td>
</tr>
<tr>
<td>Selective SNRIs (for example, duloxetine)</td>
<td>- Blocks reuptake of norepinephrine and serotonin</td>
<td>- Nausea, somnolence, dizziness, constipation - Avoid concurrent use of tramadol</td>
</tr>
<tr>
<td><strong>Anticonvulsant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentinoids, for example gabapentin and pregabalin</td>
<td>- Binds to calcium channels on peripheral nerves to reduce nerve excitability and excessive release of neurotransmitters such as glutamate - May support inhibitory pain pathways and reduce NMDA receptor activity</td>
<td>- Somnolence, dizziness, dry mouth, nausea, blurred vision - Small increase in risk of suicidal thoughts and behaviour – be alert for mood changes, distressing thoughts and feelings of self-harm - Reduced dose required in renal impairment</td>
</tr>
</tbody>
</table>

NMDA = N-methyl-D-aspartate. SNRI = serotonin norepinephrine reuptake inhibitor.

Interventional procedures (Box 2) may need to be considered for patients whose neuropathic pain remains severe after pharmacological treatments. Advances in imaging technology and equipment design have increased the range and safety of those available to manage neuropathic pain that does not respond to pharmacological approaches (Bhaskar, 2012).

Interventional procedures

Interventional procedures have specific indications for use and should be carefully considered in light of the patient’s individual circumstances. Not all may be available locally, so patients may have to travel for treatment and some may require specialist training. Anatomical changes in the patient, due to previous surgery, radiotherapy or the tumour itself may also require a change of technique or render a potentially useful intervention inappropriate.

Although interventions are only considered for pain that does not respond adequately to pharmacological approaches, if they are considered too late in a patient’s illness, the patient may not achieve the full benefit of them or may be too frail to have them. If an intervention succeeds in relieving pain, the analgesia may need to be reduced (or possibly discontinued) to prevent unwanted side-effects.

Conclusion

Neuropathic pain in patients with advanced cancer may be caused by the cancer itself, anti-cancer treatment or a co-existing condition, and is likely to present alongside other types of pain. Managing neuropathic pain in cancer often requires the use of adjuvant analgesics with more-traditional analgesics. Adjuvant analgesics are usually introduced gradually to minimize the risk of adverse effects. It may take several weeks before a desired effect is achieved and pain relief may only be partial, so it is important to keep treatment goals realistic and manage patient expectations accordingly. Consideration of interventional procedures may be needed if medications fail to provide analgesic relief.

The effect of neuropathic cancer pain on patients is multi-dimensional and, as such, best met with a multidisciplinary approach. Nurses are well placed to assess the severity of the pain and its impact on their patient’s quality of life, monitor response to treatments and ensure patients receive the right support. NT

References


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