Managing pain in advanced illness

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Pain is common in patients whose illness is advanced and impacts significantly on quality of life.[1] Despite this, pain is managed poorly across a variety of conditions, including cancer, renal failure, neurological disorders and dementia.[2–5] This reflects under-diagnosis, under-reporting, and misconceptions about analgesia by both healthcare professionals and patients.[6,7] A framework for pain assessment and treatment is outlined in this article.

Identify

Systematically asking patients about pain is key. Although this is common sense, it is not common practice. As pain is a subjective experience, the gold standard for its identification is patient self-report. Specialised tools are available for cognitively impaired patients and those with communication difficulties whose pain is often missed.[8]

Assess

The aim of assessment is to diagnose the cause(s) of pain which may reflect:

- advanced disease
- comorbidities
- iatrogenic effects
- chronic pain
- psycho-social issues.

Identification of the underlying mechanism of pain guides treatment and requires a thorough history and examination, covering:

- site
- character
- severity (worst, best and an 'average')
- onset
- duration
- radiation
- associated features
- exacerbating or relieving factors
- previous treatments
- physical and psychosocial issues.

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An exploration of the impact of the pain on the patient and their family is important, both as a therapeutic intervention and as a basis for tailoring pain management to the individual.

Pain mechanisms

Pain can be classified as nociceptive or neuropathic. Nociceptive pain results from injury to somatic or visceral structures. Neuropathic pain reflects dysfunction or damage in the peripheral or central nervous systems. Pain often arises from mixed mechanisms, yet a neuropathic component is commonly missed leading to under-treatment.[9] Neuropathic pain should be considered in diseases involving neural structures or pain that is associated with altered sensation within a neuroanatomical distribution.[10] Suggestive descriptors that may be used by patients include 'burning', 'stinging' and 'shooting'. Examination of the painful area includes testing of sensation and autonomic function.

Background or breakthrough

Background pain is persistent requiring regular analgesia. Breakthrough pain describes transient exacerbations that occur spontaneously or following a trigger, despite controlled background pain.

Assessment tools

There are a variety of patient-, disease- and pain-specific scales that can be helpful in the assessment of pain severity and in monitoring treatment response. Reliable, validated tools include:

- the numerical rating scale ('Can you rate your pain from 0 to 10, where 0 is no pain and 10 is the worst pain you have experienced?')
- the verbal rating scale ('How would you describe your pain: mild, moderate or severe?').[11]

To get a full picture, it is useful to ask the patient about their pain at worst, at best and on average or overall.

Treat

Treatment requires a multi-modal, multidisciplinary team approach (Fig 1). Where possible, target the underlying causes of pain. For 'mechanical' pain consider 'mechanical' solutions, such as minimally invasive spinal procedures to treat vertebral metastases.

Less than 50% of patients experience adequate analgesia with a single agent, and response can be determined within

Fig 1. Multimodal approach to managing pain. TENS = transcutaneous electrical nerve stimulation; WHO = World Health Organisation.

Key points

Pain is common in advanced illness but is poorly managed across a range of malignant and non-malignant conditions

Under-diagnosis of pain is a significant barrier to effective patient care and necessitates proactive, systematic screening of patients for pain

Clinical assessment should focus on identifying the underlying cause of pain and, in particular, whether it arises from nociceptive, neuropathic or mixed mechanisms

Pain management is multi-modal and needs to address the psycho-social determinants of pain and the need to educate the patient about their pain and its management. The World Health Organisation (WHO) analgesic ladder provides a framework but does not replace personalised treatment plans

Patients are at risk of treatment failure and adverse events resulting from poly pharmacy and organ impairment; regular review of management, selection of drugs in light of hepatic and renal function, and discontinuation of ineffective treatments is important

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2–4 weeks.[12] Therefore, regular review and treatment rationalisation are essential. Seek specialist advice:

> when using unfamiliar medication
> in moderate to severe renal or hepatic impairment
> if the pain is refractory to first-line treatment.

Education

Patient education can have a meaningful impact on pain. National Institute for Health and Care Excellence (NICE) opioid guidance recommends the provision of verbal and written information at the initiation of therapy.[13] Education should address fears and misconceptions about opioids and patients should be advised about triggers for treatment review, side effects and how to seek help. The target of a 50% reduction in pain intensity may not always be possible and the key is to establish mutually agreed, realistic goals.

Pharmacological approaches

The World Health Organisation analgesic ladder (Fig 2) provides a framework for initiating and titrating analgesia but does not replace personalised treatment plans. The ladder, with disease-specific modifications, has been shown to provide adequate pain control for 96% of renal failure patients and 45–100% of cancer patients, including those with neuropathic pain.[14-16]

Polypharmacy is common and up to one-third of palliative patients are at risk of significant drug interactions.[17] Several agents, including tramadol, fentanyl and some antidepressants, can cause serotoninergic syndrome if used together. Rationalise medication and maintain vigilance for adverse effects.

Step 1: non-opioid analgesia

Non-opioids improve cancer pain, but evidence regarding their additional benefit when used together with opioids is weak.[18] Combinations should be reviewed according to patient preferences and medication burden.

> Paracetamol acts centrally. Dose reductions are necessary in patients whose body weight is less than 50 kg, for malnourished patients or for those with risk factors for liver failure.
> Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase 2 (COX-2), thereby reducing inflammation-induced hyperalgesia. Owing to significant adverse effects, use the lowest dose for the minimum period and restrict use by at-risk patients. Naproxen is the NSAID of choice for those who have cardiovascular disease; diclofenac and selective COX-2 inhibitors should be avoided.[19] Low-dose ibuprofen and nabumetone have more favourable gastrointestinal profiles than do other NSAIDs. Nephrotoxicity is similar across the group. Serum creatinine may be misleading in patients with cachexia. In a study of cancer patients, 60% had impaired glomerular filtration rate (GFR) but 90% had 'normal' serum creatinine.[20] Thus GFR should be checked before and 1–2 weeks after NSAID initiation.

Step 2: 'weak' opioids (codeine, tramadol or dihydrocodeine)

> Codeine functions as a pro-drug of morphine.
> Tramadol has opioid and non-opioid analgesic properties.

- Both have ceiling doses. The following oral-dose conversions are safe and clinically useful.
  - 240 mg codeine: 24 mg morphine
  - 400 mg tramadol: 40 mg morphine.
- For rapidly escalating pain, it is reasonable to pass directly from step 1 to step 3 of the ladder.[21]

Patients should be informed that persistent constipation and transient nausea, vomiting and drowsiness are predictable opioid effects, and that regular laxatives and rescue anti-emetics will be prescribed.[13] They should also be given advice about driving when taking opioids.[13]

The overall benefit of opioids in chronic non-malignant pain is unclear. It is important that patients understand treatment goals, that non-opioid options are explored and that chronic pain services are consulted.

Step 3: 'strong' opioids (morphine, oxycodone, hydromorphone, fentanyl, buprenorphine, alfentanil or methadone)

In the absence of renal or hepatic dysfunction, morphine remains the first-line treatment because of its familiarity, availability and cost. The recommended starting dose is 20–30 mg per day with 5 mg as required. If a patient has round-the-clock background pain, regular morphine should be given as a sustained release (12 hourly) formulation. Both the regular and the supplemental analgesia should be titrated to patient need.[13, 22]

Although there is no ceiling dose, opioid escalation with transient or minimal improvements in pain should prompt treatment re-evaluation. Switching between opioids might benefit patients who are experiencing inadequate analgesia or side effects despite laxatives, anti-emetics and opioid-sparing treatment.

Transdermal fentanyl and buprenorphine 'patches' are less useful to those with unstable pain because they have long half-lives and latent periods before pharmacological steady states are reached.[22] Nevertheless, they provide a non-invasive alternative if the oral route is compromised and may be less constipating and more patient-friendly than oral opioids.[22] It is important to understand that 'low dose' patches deliver a considerable morphine equivalent dose:

- fentanyl 12 µg patch: 45 mg oral morphine daily
- buprenorphine 20 µg patch: 30 mg oral morphine daily.[13]

Organ dysfunction

There is limited evidence to guide opioid use in those who have renal and/or hepatic impairment.[22] In advanced hepatic disease, concomitant renal impairment is often more clinically significant. When GFR is less than 50 ml/min, toxic metabolites of morphine will accumulate. A reduction in dose by 75% or a switch to an alternative opioid is then required. Oxycodone is better tolerated and is used for patients with a GFR of 10–50 ml/min; below this level, lower doses and/or longer dose intervals are necessary. As alfentanil undergoes hepatic inactivation, it is the preferred regular opioid when GFR is less than 10 ml/min. Alfentanil has a high potency and short duration of action (of <10 min) requiring specialist supervision and continuous subcutaneous infusion.

Breakthrough pain

Treatment of breakthrough pain includes rescue doses of immediate release (IR) opioids, usually the same opioid

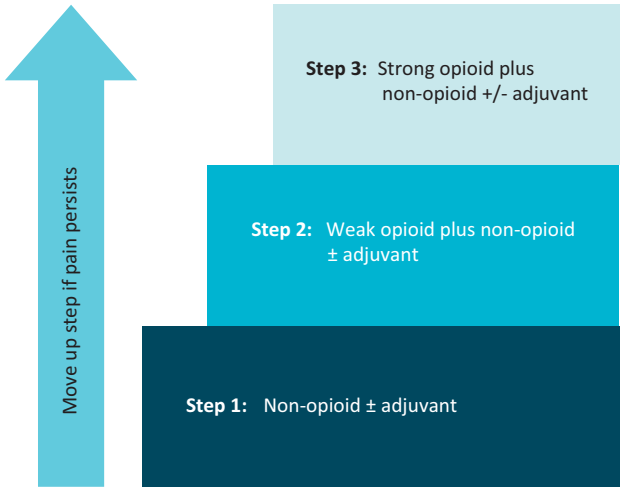

Fig 2. The World Health Organisation analgesic ladder.[27]

administered via the same route as the regular agent, and optimisation of regular analgesia. If a precipitant is predictable and unavoidable, offer IR opioids prophylactically.[23] Traditionally, a rescue dose is a percentage of regular opioid (eg one-sixth of the daily dose). This is a useful guide, but rescue dose titration should be individualised for each patient.[23] Transmucosal (buccal, sublingual or nasal) fentanyl has a quicker onset and shorter duration of action, more closely aligned to the time-profile of breakthrough pain, than standard IR opiods.[24] These agents are costly, are licensed for patients with cancer pain taking 60 mg oral morphine equivalent, and have idiosyncratic titration protocols requiring specialist initiation and supervision.[25]

Adjuvants

Adjuvants are medications that provide analgesia but have another primary indication (Table 1). Adjuvants with the most robust evidence base in neuropathic pain are tricyclic antidepressants, pregabalin and gabapentin.[10] Choice of adjuvant is guided by patient preferences and risk factors (Table 2). In predominantly neuropathic pain, consider an adjuvant as a first-line treatment; for example, duloxetine in diabetic neuropathy. Lidocaine plasters may be useful in areas of allodynia. As cancer pain often reflects mixed mechanisms, consider opioids as a first-line treatment.[9] Two-drug combinations have superior efficacy in neuropathic pain and may act synergistically. There is insufficient evidence to allow the recommendation of particular combinations, but it is prudent to avoid drugs with similar pharmacological mechanisms (ie pregabalin and gabapentin).

Interventional anaesthetic techniques

In complex pain, early anaesthetic assessment for nerve blocks, intrathecal drug delivery or percutaneous cordotomy is advocated. These approaches may improve refractory pain and allow reductions in systemic therapy, thereby minimising side effects.[26]

Table 1. Adjuvant medication and indication.

Adjuvant	Indication
Corticosteroids (dexamethasone)	Inflammatory, malignant bone or liver capsule pain
Anticonvulsants (gabapentin or pregabalin)	Neuropathic pain
Anti-depressants (amitriptyline)	Neuropathic pain
Skeletal muscle relaxants (benzodiazepines, baclofen or tizanidine)	Spasticity-associated pain
Smooth muscle relaxants (hyoscine butylbromide or nifedipine)	Colic or tenesmus oesophageal spasm
Bisphosphonates (zolendronic acid)	Malignant bone pain

Table 2. The use of tricyclic antidepressants or pre-synaptic calcium-channel-blocking anticonvulsants.

	Tricyclic antidepressants (TCAs) (amitriptyline or nortriptyline)	Pre-synaptic calcium-channel-blocking anticonvulsants (pregabalin or gabapentin)
Factors favouring use	> Lesser tablet burden > Renal impairment (caution: monitoring required) > Coexistent indication for TCA use (depression, sweating or bladder spasm) > Cost	> Epilepsy (caution: gabapentin can worsen absence seizures) > Cardiac disease (caution: pregabalin can exacerbate heart failure > Hepatic impairment > Coexistent indication – (gabapentin: hot flushes, hiccups or pruritus – pregabalin: generalised anxiety disorder)
Factors against use	> Seizures (reduced threshold) > Cardiovascular disease (dysrhythmias) > Anti-muscarinic effects (urinary retention, dry mouth and constipation) > Hepatic impairment (reduce dose or avoid) > Hyponatremia > Bipolar disorder	> Renal impairment (dose reduce or avoid) > Tablet burden > Cost > Psychotic illness (gabapentin) > Gynaecomastia

TCA = tricyclic antidepressant.

Conclusions

Good-quality pain management impacts significantly on the quality of life of patients who have advanced disease. A systematic approach to the identification and treatment of pain is required, with teams structured around evidence-based models of integrated care. As there are high failure rates with single agents, the approach should be pragmatic and multi-modal, with regular review of treatment and discontinuation of ineffective therapies. The step-wise approach of the analgesic ladder provides a useful framework for pain management, but does not replace individualised treatment plans that tailor treatment to patient preferences and risk profiles. ■

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