Management of pain in advanced disease

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Abstract

Background: Pain is common in advanced malignancy but also prevalent in other non-malignant life-limiting diseases such as advanced heart disease; end stage renal failure and multiple sclerosis. Patients with renal or liver impairment need specific consideration, as most analgesics rely on either or both for their metabolism and excretion.

Sources of data: Recent evidence-based guidelines and the systematic reviews that have informed their recommendations.

Areas of agreement: The principles of the WHO (World Health Organisation) analgesic ladder are commonly endorsed as a structured approach to the management of pain. For neuropathic pain, the efficacy of different agents is similar and choice of drug more guided by side effects, drug interactions and cost.

Areas of controversy: Evidence supporting the WHO analgesic ladder is disputed and alternatives suggested, but no overwhelming evidence for an alternative approach exists to date.

Growing points: Alternative approaches to the WHO analgesic ladder, new analgesic agents, e.g. rapid onset oral/intranasal fentanyl.

Key words: analgesic ladder, cancer, heart failure, liver failure, palliative, pain, motor neurone disease, multiple sclerosis, renal failure, human immunodeficiency virus

Introduction

Pain is defined an ‘unpleasant sensory and emotional response to a stimulus associated with actual or potential tissue damage’.1 Nociceptive pain occurs as an appropriate physiological response transmitted to a conscious level when nociceptors in bone, muscle or any body tissue are activated. Neuropathic pain is initiated as a direct consequence of a lesion or disease affecting the somatosensory system.1

It is estimated that severe cancer pain is common and affects 70–80% of patients with advanced malignant disease.2 The prevalence of pain is similar
in a number of non-malignant progressive and lifelimiting diseases: 41–77% of patients with advanced heart disease; 34–77% of patients with advanced chronic obstructive pulmonary disease; 47–50% of patients with advanced renal disease; 63–80% of patients with acquired human immunodeficiency syndrome; 50–75% of patients with multiple sclerosis; and 15–20% of patients with amyotrophic lateral sclerosis, for example.3–5

In 1986 the World Health Organisation (WHO) published *Cancer Pain Relief* to highlight the subject as an important but neglected public health issue in both developed and developing countries.6 The guideline was developed through review of published research/evidence and multinational expert consensus. As well as highlighting key barriers to achieving adequate cancer pain relief globally (such as lack of opioid availability throughout the world, and legislative and financial factors preventing appropriate use of opioids for cancer pain in many countries), the guideline also introduced a ‘method for relief of cancer pain’.6 This provided a structured approach for the holistic assessment and non-pharmacological and pharmacological management of cancer pain. As part of the pharmacological management, the concept of the ‘analgesic ladder’ was presented (Fig. 1). This was driven by the belief that most patients throughout the world could have adequate pain relief if there was a structured approach to guide use of available effective and relatively inexpensive drugs, and administer them by mouth, on a regular basis, and according to the individual needs of the patient.6,8

The original analgesic ladder was designed in the context of cancer pain, but the principles are commonly adopted in other advanced and progressive life-limiting conditions.9 There are specific considerations for some types of advanced disease. For example, choice of analgesic drug in advanced renal disease and advanced liver disease is dependent on use of analgesics less dependent on liver or renal metabolism and clearance. Certain types of pain, e.g. spasms or painful spasticity in advanced neurological disease, and, neuropathic pain (in advanced neurological disease and advanced cancer) have greater focus on adjuvant analgesics rather than opioids that form the central component of the ladder. Indeed since the original WHO analgesic ladder, the concept of a ladder has also been applied to groups of adjuvant drugs, e.g. the adjuvant analgesic ladder for neuropathic pain (10p. 293).

This paper therefore reviews the WHO analgesic ladder in the context of current evidence-based guidelines, the evidence underpinning it and areas of current debate and controversy. Management of pain in patients with significant renal and liver impairment and pain in advanced neurological disease are given specific consideration for the reasons described above. Whilst the focus of this review is pharmacological agents, non-pharmacological options to help provide analgesia, such as transcutaneous electrical nerve stimulation and acupuncture, may be considered alongside the pharmacological approach, accepting that the evidence for the non-pharmacological options is generally quite limited.11,12

Regardless of the patient’s diagnosis, pain pathway, opioid receptors and the pharmacology of analgesics used, the concept of ‘total pain’ should never be forgotten. Dame Cicely Saunders defined this as ‘the suffering that encompasses all of a person’s physical, psychological, social, spiritual, and practical struggles’.13 Unrecognized psychological, social and spiritual needs will often explain a non-responding physical pain.

![Fig. 1 The WHO analgesic ladder. Reproduced with kind permission of the WHO.](https://academic.oup.com/mbio/article-abstract/110/1/117/278138)
Pain and the analgesic ladder

The WHO analgesic ladder (Fig. 1) has been widely accepted as a framework for the initiation and titration of analgesics for cancer pain and adopted worldwide following its introduction. It is acknowledged that the research evidence demonstrating its efficacy is limited, but equally that statistically powered randomized controlled trials with this patient population are complex and difficult to achieve. The European Association of Palliative Care (EAPC) reviewed its evidence-based recommendations on pain management in 2012, and acknowledged that due to gaps and difficulties in evidence, guidelines at the present time are therefore dependent more on expert consensus.

In the traditional three-step analgesic ladder model of pain management (Fig. 1), mild pain (Step I) is treated with a non-opioid analgesic (such as paracetamol), moderate pain (Step II) with an opioid for mild-to-moderate pain such as codeine or tramadol (in addition to paracetamol) and severe pain (Step III) with an opioid for moderate-to-severe pain (such as morphine, oxycodone or fentanyl).

Adjuvant analgesics can be added at any step of the ladder: non-steroidal anti-inflammatory drugs (NSAIDs) for bone pain or liver capsule pain; anti-epileptic or anti-convulsant drugs for neuropathic pain (see later section on neuropathic pain) and steroids (such as dexamethasone) for liver capsule pain, headaches from raised intracranial pressure and pain from tissue compression or infiltration, e.g. malignant spinal cord compression. Ketamine is a dissociative anaesthetic, which has analgesic properties at sub-anaesthetic doses (thought to be through its action as an N-methyl-D-aspartate-channel blocker). It can have a role for neuropathic pain and inflammatory or ischaemic pain alongside the analgesic ladder, under specialist supervision.

NSAIDs have traditionally been used widely as adjuvant analgesics but in recent years their use has reduced through realization of their significant renal, gastrointestinal (GI) and cardiovascular morbidity and mortality. The potential for detrimental effect on renal function is similar between different NSAIDs and not therefore a discriminatory factor when choosing between them. Naproxen has a high risk of GI toxicity but preferable for patients with cardiovascular risk and ibuprofen has a low GI risk at low doses but high cardiovascular and stroke risk.

Opioids and the analgesic ladder

The distinction between opioids as being ‘weak’ or ‘strong’ is somewhat arbitrary: high-dose codeine is comparable to low-dose morphine and vice versa, for example. Note that codeine is metabolized to codeine-6-glucuronide and also to morphine, via the CYP2D6 enzyme. Due to genetic polymorphism of CYP2D6 across the population (particularly between different ethnic groups), there is a wide inter-individual variation in conversion to morphine (and therefore analgesic effect of codeine).

Tramadol has both opioid and non-opioid properties, the later through activating descending anti-nociceptive pathways in the spinal cord via inhibition of serotonin and noradrenaline reuptake, and stimulating pre-synaptic serotonin release. This may therefore explain its effect in some studies on neuropathic pain, but also means that it has a potential for CNS adverse effects. In particular, if used with another drug which affects serotonin metabolism it can lead to serotonin toxicity.

In the EAPC review of the evidence, they noted some evidence for ‘low-potency’ opioids in the above stepwise approach and that the limited available evidence suggested no overall difference in efficacy between tramadol, codeine plus paracetamol and hydrocodone plus paracetamol. They also noted that ‘oral morphine at low doses can be used in opioid naïve cancer patients’. The current EAPC recommendations therefore suggest that for patients with mild-to-moderate pain, or when pain is not controlled with paracetamol or a non-steroidal anti-inflammatory drug, consider a Step II opioid (such as codeine or tramadol) or a low-dose Step III opioid (such as morphine or oxycodone).

Morphine has traditionally been the first-choice drug for treating severe (cancer) pain. Current EAPC recommendations state that available evidence shows no significant difference between morphine, oxycodone and hydromorphone given by the oral.
route, recommending any of these three drugs can be used as the first-choice Step III opioid.\(^2\) Note that by mouth oxycodone has a bio-availability of 60–87%, whereas for morphine it is 15–64%, and a lower oral dose is therefore needed than that of morphine to have a comparable analgesic effect (many guidelines therefore give the oral potency ratio for oxycodone to morphine as 1.5:1).\(^10\)

A systematic review of Step III opioid dose titration suggests a starting oral morphine dose of 30 mg in 24 h for opioid naïve patients and 60 mg in 24 h for patients already using a WHO Step II opioid.\(^19\) It is important to anticipate common side effects when initiating an opioid: constipation, nausea and drowsiness. All patients initiating a strong opioid should be given a laxative and should be advised that they may have transient nausea (which may therefore require an anti-emetic if persisting).\(^20\) Patients should also be advised that they may experience drowsiness or reduced concentration when starting strong opioid treatment or at subsequent dose increases, which is often also transient.\(^20\)

Transdermal opioid patches are considered separately in the current EAPC guidelines, but the recommendations acknowledge that they may be preferred to other Step III opioids for some patients. There is an argument that they should be considered along with other first-line strong opioids citing evidence from a small number of un-blinded studies that support patient preference and low incidence of constipation with transdermal opioids.\(^2\) Current National Institute for Health and Care Excellence (NICE) guidelines in the UK do not advocate first-line use of transdermal opioid patches.\(^21\) Commonly cited reasons for this include long latent period before a pharmacological steady state is reached, and, difficulty or delayed titration (every 3 days, because of the drug half-life).\(^2\) Indeed, there is a wide variability in the pharmacokinetics, for transdermal fentanyl for example, the onset of action is 3–23 h, time-to-peak plasma concentration of 24–72 h and plasma half-life (after a patch has been removed and not replaced) of 13–22 h.\(^10\) These factors and the relative potency of fentanyl have not always been well recognized by healthcare professionals prescribing them. After reported life-threatening adverse reactions and death after fentanyl overdose in patients using the patches for malignant and non-malignant pain drug alerts/safety updates have been issued in a number of countries.\(^10,22\)

A systematic review of transdermal opioids as front-line treatment of moderate-to-severe cancer pain concluded that on the basis of current evidence oral morphine probably remains the treatment of choice for moderate-to-severe cancer pain in opioid naïve cancer patients but that transdermal opioids represent a valid alternative when the oral route or oral morphine are not suitable.\(^23\)

Transdermal opioids may therefore be preferable in certain clinical circumstances, e.g. poor patient compliance with oral medication; poor GI drug absorption/malabsorption; dysphagia and difficulty swallowing oral preparations (e.g. head and neck cancer, advanced stages of dementia, other neurodegenerative diseases) and in renal impairment.\(^9\) The equivalent potency of transdermal opioid preparations are summarized in Table 1 and the relative potency of fentanyl should not be underestimated. A low-dose buprenorphine patch is generally more appropriate in an opioid naïve patient with advanced dementia and dysphagia or non-compliance with oral medication. For patients with rapidly escalating pain and/or additional end of life symptoms opioid administration via a syringe driver is generally more appropriate.

The benefit of use of paracetamol with Step III opioids (advocated in the original WHO analgesic ladder) has also been the subject of review.\(^24\) The rational being that additional paracetamol may increase pain relief offered by opioids alone, or reduce opioid-related side effects in patients with poor pain relief and excessive side effects from opioids.\(^24\) One systematic review found five studies, of varying methodological quality, which explored the effect on pain of paracetamol used in addition to a Step III opioids. Of those only one found a marginal analgesic advantage of combining paracetamol, and the doses used in that study (up to 5 g per day) were higher than those commonly used in clinical practice.\(^25\) However, the authors of the systematic review also noted that in some of the studies baseline pain intensity was too low to permit the detection of clinically significant changes and therefore concluded that the clinical practice implications of their review are limited by
lack of more direct evidence. A systematic review by different authors arrived at similar conclusions. At present paracetamol continues to be commonly used in clinically practice in addition to Step III opioids, although the evidence for this may be ‘weak if any’. This should perhaps therefore be considered on an individual patient basis, with attention to their subjective benefit from the addition of paracetamol and review of whether it should continue, particular if of no clear additional benefit to the individual and causing an added tablet burden.

**Opioid switching** is defined as ‘the clinical practice of substituting one Step III opioid with another when a satisfactory balance between pain relief and adverse effects is not achieved with appropriate titration of first opioid’. It is recommended in patients where side effects are severe, unmanageable and preventing opioid dose escalation. This is most commonly from morphine to another Step III opioid.

Current guidelines recommend the following conversion ratios between opioids:

- oral morphine/1.5 = oral oxycodone (manufacturer’s recommendation 2:1),
- oral morphine mg/100 = transdermal fentanyl mg in 24 h (manufacturer’s recommendation 150:1),
- oral codeine/10 = oral morphine,
- oral tramadol/10 = oral morphine,
- oral morphine/3 = subcutaneous diamorphine,
- oral morphine/2 = subcutaneous morphine,
- oral oxycodone/1.5 = subcutaneous oxycodone,

For example, a total daily oral morphine dose of 60 mg is approximately equivalent to 40 mg of oxycodone daily or a 25 µg per h fentanyl transdermal patch. A number of online opioid dose converter guides/tools are available (such as www.book.pallcare.info). For patients unable to receive opioids by the oral or transdermal route, the subcutaneous route is the first choice alternative.

**Breakthrough pain** may be defined as pain ‘characterized by transient exacerbations of pain that occur on a background of stable pain otherwise adequately controlled by around-the-clock opioid therapy’. In recent years, a number of immediate-release oral, buccal and sublingual fentanyl preparations have become available specifically for breakthrough pain. Traditionally, the breakthrough pain dose has been calculated as the 4 hourly equivalent dose of the background Step III opioid (e.g. oral morphine immediate-release liquid dose calculated as 1/6th of the total daily dose of prolonged release morphine tablets). More recently, some guidelines recommend using 1/10th to 1/6th; however, it is recognized that a standard fixed dose will not suit all patients and the breakthrough dose should be individualized, using

<table>
<thead>
<tr>
<th>Transdermal opioid patch</th>
<th>Conversion ratios</th>
<th>Approximate equivalent dose of oral morphine over 24 h (mg)</th>
<th>Opioid dose calculator suggested equivalent dose of oral morphine over 24 h(^9) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine 5 µg/h 7-day patch</td>
<td>75–115:1(^a)</td>
<td>9–12</td>
<td>12</td>
</tr>
<tr>
<td>Buprenorphine 10 µg/h 7-day patch</td>
<td>100:1(^b)</td>
<td>18–27.6</td>
<td>24</td>
</tr>
<tr>
<td>Buprenorphine 20 µg/h 7-day patch</td>
<td>36–55.2</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine 35 µg/h 4-day patch</td>
<td>75–115:1(^a)</td>
<td>63–96.6</td>
<td>84</td>
</tr>
<tr>
<td>Buprenorphine 52.5 µg/h 4-day patch</td>
<td>100:1(^b)</td>
<td>94.5–144.9</td>
<td>126</td>
</tr>
<tr>
<td>Buprenorphine 70 µg/h 4-day patch</td>
<td>126–193.2</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>Fentanyl 12 µg/h 3 day patch</td>
<td>100:1(^b)</td>
<td>28.8–43.2</td>
<td>43.2</td>
</tr>
<tr>
<td>Fentanyl 25 µg/h 3 day patch</td>
<td>150:1(^b)</td>
<td>60–90</td>
<td>90</td>
</tr>
<tr>
<td>Fentanyl 50 µg/h 3 day patch</td>
<td>120–180</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Fentanyl 75 µg/h 3 day patch</td>
<td>180–270</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>Fentanyl 100 µg/h 3 day</td>
<td>240–360</td>
<td>360</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Manufacturer’s recommendation.
these ratios as a starting reference point. Oral immediate-release opioids or buccal or intranasal fentanyl preparations are all advocated for breakthrough pain. There is some evidence, that for some patients, the buccal or intranasal fentanyl preparations may provide a more rapid onset of action and shorter duration of effect. This is currently debated, particularly as a number of the fentanyl studies are placebo controlled (rather than compared with oral immediate-release morphine liquid as the current ‘gold standard’) and the potential publication bias from studies sponsored by the pharmaceutical industry. In the UK NICE do not recommend using oral fast-acting fentanyl products first-line without specialist advice.

Interventional pain management (such as peripheral nerve blocks, epidural and intrathecal infusions and plexus blocks) should be considered alongside the conventional analgesic approach and are often underused or considered too late. They are also dependent on available local expertise.

Opioid-induced hyperalgesia (OIH) is defined as a state of nociceptive sensitization caused by exposure to opioids. The underlying mechanism is not well understood but clinically it may manifest as rapid tolerance to opioids, increasing pain despite increasing opioid doses and pain becoming more diffuse and extending beyond the distribution of the pre-existing pain. The incidence of OIH is not known and care needs to be taken to not diagnose increased pain from disease progression or opioid tolerance as OIH. The management of OIH involves reducing the opioid felt to be causal and consideration of switching to an opioid with less potential for OIH (such as methadone or buprenorphine), maximizing non-opioid analgesia (such as paracetamol, NSAIDs) and consideration of the addition of ketamine.

Pain in the presence of renal impairment

Use of opioids in patients with significant renal impairment warrants specific consideration. This may apply to patient with pain and end-stage renal disease or patients with cancer who have concurrent renal impairment. Current guidelines advocate the use of estimated glomerular filtration rate (eGFR) to stratify degree of renal impairment, as opposed to the traditional measurement of serum creatinine. However, the use of eGFR as a measure of renal function is less accurate in the presence of oedema, cachexia, low protein states and acute renal failure, which is particularly relevant in the context of patients with advanced cancer and renal impairment.

Structural differences between opioids result in significant differences in pharmacokinetic parameters and therefore their pharmaco-dynamic effects in renal failure. Morphine is associated with an increased risk of adverse effects in patients with renal impairment as several of the metabolites are active, particularly M6G. Codeine produces its analgesic effect partly through biotransformation to morphine, and its pharmacologically active metabolites therefore accumulate in renal impairment.

Tramadol is metabolized by the liver to an active metabolite and unchanged tramadol and its metabolites are predominantly excreted in the urine. While the elimination half-life of tramadol is increased in patients with renal impairment, it is potentially the least problematic opioid at Step II of the WHO ladder.

For oxycodone there is a prolongation of elimination half-life when used in renal failure (of oxycodone itself and its metabolites). Elimination of fentanyl occurs by initial redistribution and then biotransformation to metabolites and subsequent renal excretion, none of its metabolites appear to have significant pharmacological activity.

Methadone is primarily excreted in the faeces and is not dependent on the kidney for its elimination or that of its metabolites.

For buprenorphine there is inconsistency/insufficient evidence in relation to use in patients with renal impairment.

Current guidelines therefore recommend that fentanyl and methadone are the most preferable Step III opioids and tramadol for Step II. It is however acknowledged that methadone should only be used under experienced specialist supervision (even in the absence of renal failure) and that it may not always be appropriate or practical to use fentanyl formulations, in which case alternative opioids at reduced
doses and reduced dosing frequency should be considered (see Table 2).

**Pain in the presence of liver impairment**

There has been a dramatic increase in the prevalence of liver disease over the last few decades. The effect of liver impairment is relevant to the topic of pain in advanced disease from two perspectives. First, in the context of patients with advanced malignancy and liver impairment (e.g. from metastatic liver disease), and, secondly from those with primary liver disease itself (e.g. alcoholic liver cirrhosis). In the latter group pain is as common a symptom as in patients with advanced cancer, and more common than that reported from patients with advanced heart failure or chronic obstructive pulmonary disease.

The liver plays a key role in drug metabolism and elimination, which is dependent on hepatic blood flow, hepatic enzyme capacity and plasma protein binding. Drug metabolism in the liver generally occurs via three mechanisms: oxidation/reduction/hydrolysis reaction of the hepatic cytochrome P450; conjugation and biliary excretion and elimination.

The major metabolic pathway for most opioids is oxidation and therefore a greater risk of drug accumulation secondary to reduced drug metabolism. Morphine (and buprenorphine) being the notable exception (as it primarily undergoes glucuronidation) theoretically suggesting that it may be the preferable opioid in this context. In addition, some analgesics are dependent on the liver for transformation into their active metabolites (codeine into morphine for example) and the analgesic action of these drugs may therefore be reduced in this context.

Few clinical studies have evaluated the safety of various analgesics in patients with advanced hepatic dysfunction, and some of the evidence that does exist is contradictory. Furthermore, whilst there are measurable parameters that can be used to guide dose adjustment in renal impairment (e.g. eGFR), there are no endogenous markers for hepatic clearance that can be used as a guide for drug dosing. The use of the Child-Pugh classification to grade severity of liver disease may help guide drug dose adjustment (based on serum bilirubin; serum albumin; prothrombin time; presence or absence of encephalopathy and presence or absence of ascites), particularly where the score is ‘C’, i.e. severe. Cirrhotic patients often have low serum protein and albumin concentrations, which in turn can lead to increased levels of free drug if the drug is highly protein bound.

As a general principle either reduced maximum dose and/or increased dose intervals (1.5–2 fold increase suggested) are recommended for all commonly used analgesics. It is preferable to avoid administration by the transdermal route as drug absorption from that route could be very variable/unpredictable. Specific prescribing guidance for patients with liver impairment in summarized in Table 3.

**Pain in advanced neurological disease**

A number of progressive and incurable neurological conditions may be associated with spasticity from upper motor neurone syndromes and muscular pain or spasms from peripheral musculoskeletal conditions.

Baclofen, dantrolene and tizanidine are commonly used for the treatment of spasticity, as well as benzodiazepines. The mechanism of action is thought to be different: baclofen blocks pre- and post-synaptic gamma-aminobutyric acid receptors; tizanidine is a centrally acting agonist of alpha-2 receptors and dantrolene directly inhibits muscle contraction by decreasing the release of calcium from skeletal muscle sarcoplasmic reticulum. Other medication used to treat spasticity (but not formally licenced for this indication) include benzodiazepines, clonidine, gabapentin and botulinum toxin.

There is little data regarding comparative efficacy and safety of the different drug options. There is ‘fair’ evidence that baclofen, tizanidine and dantrolene are effective compared with placebo in patients with spasticity and that baclofen and tizanidine are roughly equivalent for efficacy. Overall, the rate of adverse effects between tizanidine and baclofen is similar, tizanidine is associated with more dry mouth and baclofen with more weakness. As dantrolene acts directly on the skeletal muscle (rather than a central action), it produces fewer central side effects.
### Table 2 Modified drug doses for the WHO analgesic ladder in patients with renal impairment

<table>
<thead>
<tr>
<th>Analgesic ladder</th>
<th>Common analgesic drugs used and dose modification required depending on GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td>GFR &gt;50: 100% of normal dose 4 hourly</td>
</tr>
<tr>
<td>Aspirin (avoid if possible)</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>GFR &gt;50: 100%</td>
</tr>
<tr>
<td>Codeine (avoid if possible)</td>
<td>100% of normal dose 6 hourly</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>GFR &gt;50: 100% normal dose</td>
</tr>
<tr>
<td>Methadone</td>
<td>100%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>100%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>100%</td>
</tr>
<tr>
<td>Morphine (avoid if possible)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Botulinum toxin injections are largely reserved for the treatment of contractures. Cannabinoids may be considered for refractory spasticity in multiple sclerosis (and intractable cancer pain). A systematic review of cannabinoids as analgesics for postoperative and cancer pain found that they were not more effective than codeine 60 mg, but had more side effects. There is some evidence from randomized controlled trials of a modest benefit in intractable cancer pain and neuropathic pain when used in combination with maximized conventional analgesia, although this would not currently be part of guideline-based practice.

Neuropathic pain can be a particular problem in advanced neurological disease but is not exclusive to non-malignant neurological disease (e.g., pain from metastatic malignancy causing spinal cord compression). A number of drugs are advocated for the management of neuropathic pain. The evidence for some of them is weak and complicated by varying definitions of neuropathic pain in research studies and lack of placebo-controlled studies (particularly in cancer-related neuropathic pain). For those with the better evidence, the number needed to treat for commonly used neuropathic adjuvants is similar, but they have different adverse effects, drug interactions and side effect profiles, which may guide choice of drug more than difference in efficacy.

In non-cancer neuropathic pain, adjuvant drugs with the strongest evidence of effectiveness are tricyclic antidepressants (TCAs), such as amitryptiline and imipramine and anti-epileptics such as gabapentin and pregabalin. TCAs inhibit pre-synaptic reuptake of serotonin and noradrenaline in spinal pain pathways. Tertiary amine TCAs such as amitryptiline and imipramine are associated with more anti-muscarinic and sedating adverse effects than secondary amine TCAs such as nortriptyline. Anti-epileptic such as gabapentin and pregabalin inhibit the release of excitatory neurotransmitters.

Most current guidelines recommend using gabapentin/pregabalin or amitryptiline/nortriptyline and combining a lower dose of one of each group if dose titration of one is limited because of side effects. The preferable choice will depend on the individual patient. For example, a patient who is depressed with poor sleep and neuropathic pain may be more suited to using a TCA, whereas patients with a known cardiac arrhythmia (contra-indicating a TCA) and significant anxiety as well as neuropathic pain may be more suited to pregabalin. The use of adjuvant analgesics in addition to opioids for cancer pain appears to have a smaller effect than that seen in patients with non-cancer neuropathic pain.

### Table 3 Use of analgesics in patients with liver impairment

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>Use with maximum 2–3 g per day (rather than 4 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Use with caution (reduced dose and greater dose intervals): morphine, fentanyl. Less favourable alternatives: alfentanil, hydromorphone, oxycodone</td>
</tr>
<tr>
<td>Preferable to avoid: codeine, pethidine</td>
<td></td>
</tr>
<tr>
<td>Conflicting current guidance/insufficient data: buprenorphine, tramadol, methadone</td>
<td></td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>Ibuprofen’s pharmacokinetics not changed in moderate–severe liver disease, half-life of naproxen increased and usual dose should be halved</td>
</tr>
<tr>
<td>However, avoid all if possible, particularly if established cirrhosis (because of risk of hepatorenal syndrome and bleeding with co-existing thrombocytopenia and coagulopathy)</td>
<td></td>
</tr>
<tr>
<td>Neurpathic agents</td>
<td>Gabapentin and pregabalin: not dependent on liver metabolism or bound to plasma proteins; therefore, most preferable options</td>
</tr>
<tr>
<td>TCAs: if have to be considered start at a low dose. Nortriptyline and desipramine preferable to other TCAs</td>
<td></td>
</tr>
</tbody>
</table>

Effects, e.g. unacceptable drowsiness. Botulinum toxin injections are largely reserved for the treatment of contractures.
Assessment of pain in advanced neurological disease where there is reduced verbal and non-verbal communication is an additional challenge (such as advanced motor neurone disease, advanced multiple sclerosis and advanced dementia). Non-verbal pain assessment tools should be considered in these circumstances, and are most widely studied in the context of advanced dementia (for which there are a number of published reviews and systematic reviews). There is no firm conclusion to exclusively recommend one pain assessment tool over another and whilst some have better evidence they may be less user friendly in the real clinical context compared with a research study. The DOLOPLUS2, PACSLAC and PAINAD are all commonly advocated. It should be recognized that all these tools have limitations: most are actually measuring distress of which pain may be one of a number of potential causes (for example, hunger, thirst or anxiety may be expressed with similar behavioural changes). Furthermore, there is considerable variability between patients with dementia in their behavioural expression of pain, e.g. one patient may become withdrawn and refuse to eat as opposed to another who may become aggressive and verbally abusive: these patterns of behaviour could both indicate the presence of pain, but not be represented easily in a tool to quantify pain-related behaviour.

Conclusion

Pain is common in advanced malignant and non-malignant disease. Accepting its limitations, the WHO ladder provides a structured approach to pain management in advanced disease. For patients with significant renal impairment, tramadol, fentanyl and methadone are the preferred opioid options (or other opioids at reduced doses and increased dose frequencies). For patients with significant liver impairment, morphine and fentanyl are potentially the preferable opioids (or other opioids at reduced doses and increased dose frequencies). TCAs such as nortriptyline and anti-epileptics such as gabapentin have similar efficacy for neuropathic pain, the choice of drug being more dependent on side effects, drug interactions and cost. The concept of total pain and the use of non-pharmacological approaches to pain management should not be overlooked in the approach to the patient with pain in advanced disease.

References

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