PAIN MANAGEMENT AT THE END OF LIFE

Dr Peh Tan Ying

ABSTRACT

Pain is a common symptom among populations with life-limiting illnesses. Like all clinicians, family physicians involved in the care of these patients should acquire the skills and knowledge required to provide good pain control in order for the patients and their caregivers to achieve optimal quality of life. This paper is a review and presentation of the definition, classification, assessment and management of pain at the end of life based on available guidelines and evidence.

Keywords:
Pain; Analgesics; End of Life; Life-limiting Illnesses

INTRODUCTION

Pain is a highly prevalent symptom at the end of life regardless of diagnosis or setting. At least 70 percent of patients with advanced cancer experience moderate to severe chronic pain.[1,2] It is also prevalent among patients with non-cancer life-limiting conditions such as heart failure, end-stage renal disease and neurological diseases including dementia. If unrelieved, pain can lead to great distress and poor quality of life for patients and their caregivers. Pain relief can be adequately achieved in the majority of patients when well-established treatment guidelines for cancer pain are followed. Despite this, it is recognised that pain is undertreated for various reasons, including clinician-, patient- and system-related barriers.

DEFINITION AND CLASSIFICATION OF PAIN

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[3] Pain can be classified into nociceptive pain and neuropathic pain.[4] Nociceptive pain is pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors, occurring with a normally functioning somatosensory nervous system. It can be further classified into somatic pain or visceral pain. Somatic nociceptive pain involves injury to skin and deep tissue. It is often described by patients as "aching", "stabbing", "throbbing" or "pressure-like" in quality. Visceral nociceptive pain involves injury to internal organs. It is usually characterised as "gnawing" or "crampy" when arising from the obstruction of a hollow viscus (e.g. intestinal obstruction), and

PEH TAN YING
Consultant
Division of Palliative Medicine
National Cancer Centre Singapore

as "aching" or "stabbing" when arising from other visceral structures, such as organ capsules, myocardium or pleura.[4] Nociceptive pain usually responds well to opioids.

Neuropathic pain, on the other hand, is pain caused by a lesion or disease of the somatosensory nervous system. It is often described as "shooting", "pins and needles", "poking", "burning" or "like electric currents". There are often associated sensory abnormalities on examination such as allodynia, paraesthesia or hyperalgesia. Adjuvant analgesic drugs are often required for adequate control of neuropathic pain as it is commonly only partially responsive to opioids.

In cancer patients, pain can be grouped into four causal categories:[4]
• Cancer (e.g. soft tissue, visceral, bone, neuropathic);
• Treatment (e.g. chemotherapy-related mucositis);
• Debility (e.g. constipation, pressure sores); or
• Concurrent disorders (e.g. spondylosis, osteoarthritis)

PAIN ASSESSMENT

The cornerstone of adequate pain management is a comprehensive pain assessment. This is essential for two reasons: (i) to define the aetiology of pain so that appropriate treatment can be given, and (ii) to monitor response to treatment. A full pain assessment should include a complete history, physical examination, and relevant investigations where indicated. As pain is a subjective sensation, a patient's report of pain is the gold standard for assessment. It is well worth the time and effort to obtain an accurate pain history, taking into account the location, onset, quality, aggravating and relieving factors, radiation, severity and timing of pain. A review of medications is also warranted, together with assessing the impact of pain on the patient's mood, function and sleep, as well as caregivers' coping and well-being.

A useful mnemonic for taking a pain history is SOCRATES.
• S – Site: where is the pain?
• O – Onset: when did the pain start, and was it sudden or gradual?
• C – Character: What is the pain like (e.g. aching, stabbing, burning)?
• R – Radiation: Does the pain radiate anywhere?
• A – Associations: Are there any other signs or symptoms associated with the pain?
• T – Time course/treatment tried: Does the pain follow any pattern (e.g. worse at night)? Have you tried any treatment for the pain and did it work?
• E – Exacerbating/relieving factors: Does anything make the pain better or worse?
• S – Severity: How bad is the pain?

There are several pain assessment tools available for use in palliative care patients that can be used to measure pain intensity. These include:
• Visual analogue scale (VAS);
• Categorical verbal rating scales – none, mild, moderate, severe; and
• Numerical rating scale (NRS) – 0 to 10.

Special effort needs to be made to assess pain in cognitively impaired or uncommunicative patients. The PAINAD (Pain Assessment in Advanced Dementia) is a behaviour-observation pain assessment instrument developed for use in uncommunicative patients such as those whose dementia is so advanced that they are unable to verbally communicate pain.[5]

At the end of the pain assessment, several questions should be answered:
1. What is the likely cause of the pain?
2. What type of pain is it – nociceptive, neuropathic or mixed?
3. Is the pain causing psychological distress?
4. Is the pain having a negative impact on the patient's family or caregivers?

PAIN MANAGEMENT

An effective strategy for pain management at the end of life is based on several broad principles:
1. A detailed assessment of the pain should be performed initially; careful reassessment is indicated whenever a change occurs. The initial assessment always includes a history and examination, and often requires imaging or laboratory tests.
2. Pain may be addressed by disease-modifying therapy and other interventions directed against the aetiology of the pain, such as radiation therapy, surgery or, in some cases, chemotherapy.
3. Whether or not disease-modifying therapy is possible, a large proportion of patients with pain due to active cancer require symptomatic treatment.

Pharmacotherapy is the mainstay of treatment for pain at the end of life. There are three broad categories of analgesic medications: opioids, non-opioid analgesics and adjuvant analgesics. Most adjuvant analgesics are commercially available for indications other than pain but are analgesic in specific circumstances.[6]

The principles governing analgesic use include:[7]
• By the mouth – the oral route is the standard route for analgesics, including morphine and other strong opioids.
• By the clock – persistent pain requires preventive therapy. Analgesics should be given regularly and prophylactically; as needed (prn) medication alone is irrational and inhumane.
• By the ladder – use the analgesic ladder (see below). If, after optimising the dose, a drug fails to relieve pain, move up the ladder, not sideways in the same efficacy group.
• Individualised treatment – the right dose is the one which relieves the pain; doses should be titrated upwards until the pain is relieved or undesirable side effects prevents further dose escalation.
• Use of adjuvant drugs – in the context of the analgesic ladder, these include other drugs which relieve pain in specific situations.

WHO Analgesic Ladder
The World Health Organisation (WHO) developed guidelines for the management of cancer pain in the mid-1990s. In the absence of guidelines for pain management in the non-cancer population, the WHO Pain Relief Ladder has been applied to the management of pain in other diseases as well (Figure 1). The WHO recommends a stepwise approach to pain management, with the choice of analgesic based on pain severity: using non-opioids (paracetamol or non-steroidal anti-inflammatory drugs) for mild pain; mild opioids (e.g. tramadol, codeine) for mild to moderate pain; and strong opioids (e.g. morphine, oxycodone, fentanyl) for severe pain.[8] At any step of the ladder, an adjuvant analgesic can be prescribed if it can offer additional benefit in optimising pain control.
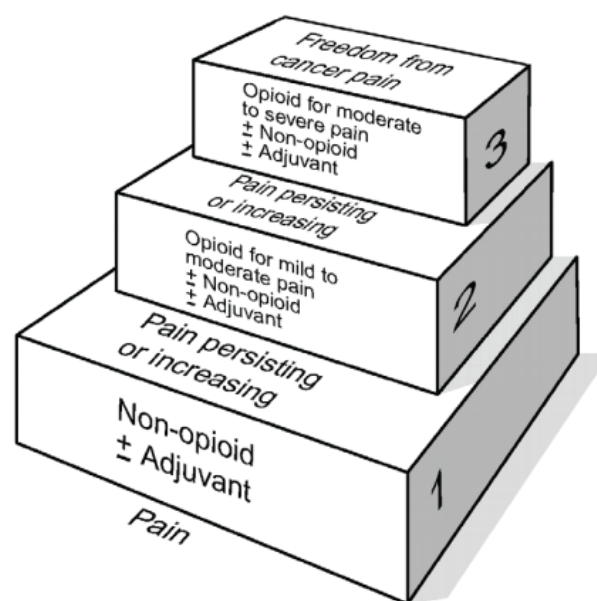

Figure 1: WHO analgesic ladder

Step 1: Non-opioid analgesics
Paracetamol is a useful analgesic for mild pain. To reduce the risk of hepatotoxicity, dosages should not exceed 4000mg every 24 hours. In a patient with severe liver impairment, lower dosages (up to 2000mg every 24 hours) may be used.[9] NSAIDs are, by definition, anti-inflammatory analgesics, and are hence of particular benefit for pains associated with inflammation. Due to the risk of cardiovascular, gastrointestinal and renal toxicity, it is advisable that as a general rule, the lowest effective dose should be used for the shortest possible length of time. Cyclooxygenase-2 (COX-2) selective inhibitor NSAIDs were introduced in the hopes of mitigating traditional NSAID-related adverse events such as gastrointestinal bleeding.[10] However, the protection afforded by COX-2

selective inhibition against gastrointestinal bleeding is not complete, and other NSAID-related toxicities are no different with COX-2 inhibitors.[11]

Step 2: Mild opioids

Opioid analgesics are the mainstay of the treatment of moderate to severe pain in patients with advanced illness. When considering starting a patient on opioids for the treatment of pain, several factors must be considered, including the severity of pain, end organ function, patient age, and history of opioid use. These factors will influence the initial opioid to be used, the starting dose, and the interval of administration.

For moderate pain, a mild opioid such as tramadol or codeine phosphate can be used. Codeine acts mainly as a pro-drug of morphine, with 2–10 percent of codeine biotransformed to morphine. Genetic polymorphism of the CYP2D6 enzyme results in significant inter-individual variability in the production of morphine, which may lead to differences in patient response. It is bad practice to prescribe codeine to patients already taking morphine; if a greater effect is desired, the dose of morphine should be increased. The maximum dose of codeine is 360mg per day.

Tramadol is a synthetic centrally acting analgesic with both opioid and non-opioid properties, and is available both as capsules and tablets that can be broken. The maximum dose is 400mg per day (100mg qds). It should be used with caution in patients with seizures, raised intracranial pressure, and severe renal or hepatic impairment, as well as those taking medication which lowers seizure threshold, such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).[12]

Step 3: Strong opioids

For severe pain, a strong opioid should be prescribed regularly. If a patient presents in severe pain, the clinician should consider whether the patient would benefit from inpatient admission to allow more rapid titration of opioids because the medications can be administered parenterally (intravenously or subcutaneously) and may be repeated and increased over minutes to hours.[13] Among the strong opioids, there is no uniformly preferred agent and there is substantial individual variation in the response to these drugs. The selection of one drug over another is typically based on clinical judgement and factors such as formulary access and cost.[7] However, morphine is generally the opioid of first choice due to availability and low cost.

MORPHINE

Morphine is the prototype opioid drug for moderate to severe cancer pain on the third step of the WHO ladder and is usually considered the standard for comparison. Morphine is primarily metabolised in the liver. It is well tolerated in patients with mild to moderate hepatic impairment;[14] glucuronidation is rarely impaired except in severe hepatic impairment.[15] The major metabolites of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), are excreted renally. M6G contributes substantially to the analgesic effect of morphine, and can cause nausea and vomiting, sedation and respiratory depression.[16] Both metabolites accumulate in renal failure, resulting in a prolonged duration of action, with a risk of severe sedation and respiratory depression if the dose or frequency of administration is not reduced. Hence, morphine should be administered cautiously in the setting of renal insufficiency, and if fluctuation in renal function can be anticipated, morphine may not be the preferred opioid given the risk of changes in effects and side effects as metabolite accumulation occurs.[17]

In Singapore, morphine is available in oral and injectable formulations. Oral morphine is available in two forms:
• Normal-release morphine sulphate solution (commonly known as mist morphine) – onset of action 30 minutes; lasts 4 hours.
• Sustained-release morphine sulphate tablet (commonly known as MST) – onset of action 2–3 hours; lasts 12 hours; available as 10mg and 30mg tablets; cannot be crushed or pounded.

Morphine sulphate tablets provide continuous analgesia with twice-daily dosing, while mist morphine is short-acting. When starting a patient on morphine for the first time, the oral short-acting formulation should be selected as it allows for active titration. When prescribing morphine for the first time, it is good practice to explain to the patient the possible side effects. In addition, it is important to always prescribe breakthrough doses and regular laxatives. An anti-emetic may be prescribed on a prn basis.

How to start and titrate oral morphine for an opioid-naïve patient:[4]
• The starting dose of mist morphine is 2.5–5mg q4H regularly round the clock, with q1H prn breakthrough doses of equal amount.
• After 1–2 days, adjust the dose upwards if the patient still has pain or is using two or more prn doses per day.
• Continue q4H regularly with q1H prn doses of equal amount.
• Increase the regular dose by 30–50 percent every 2–3 days until there is adequate relief throughout each 4-hour period.
• When the q4H dose is stable, replace with sustained release morphine sulphate tablets q12H, calculated using the same total daily dose of q4H morphine. For example, mist morphine 10mg q4H = 60mg per day = MST 30mg q12H.
• Continue to provide mist morphine for prn (breakthrough) use; give the equivalent of a q4H dose, i.e. 1/6 of the total daily dose. For example, for MST 30mg q12H, the breakthrough dose of mist morphine is 10mg q1H prn.

How to start oral morphine for a patient already on regular mild opioid:
• Take into account the morphine equivalent of the current mild opioid
• Codeine : morphine = 10 : 1

- Tramadol : morphine = 5 : 1
- Examples:
  Codeine 60mg QDS = 240mg/24h = morphine 24mg/24h
  Tramadol 100mg TDS = 300mg/24h = morphine 60mg/24h
- If the patient is still in pain, the starting dose of morphine should be calculated to give a greater analgesic effect than the medication already in use. Example:
  If a patient is on tramadol 100mg TDS but still in pain -> prescribe mist morphine 15mg q4H + 15mg q1H prn

In some clinical situations, parenteral morphine is preferred over oral administration:
- Inability to swallow (e.g. drowsiness, vomiting, severe dysphagia);
- Last few days of life;
- Severe pain requiring rapid titration;
- Unreliable GI absorption (e.g. intestinal obstruction, gastric outlet obstruction); or
- Pill burden.

Parenteral morphine can be given intravenously or subcutaneously as a continuous infusion via an infusion pump or a portable syringe driver, with breakthrough doses given by the same route.

Many patients and families have reservations about using morphine due to common misconceptions and fear of side effects (Tables 1 and 2). It is therefore prudent to address these prior to starting morphine to achieve compliance and subsequent satisfactory symptom control.

ALTERNATIVE STRONG OPIOIDS

There are multiple opioid receptor subtypes in the central nervous system and elsewhere, including the dorsal horn of the spinal cord; μ, κ and δ opioid receptors are all involved in analgesia. Opioids differ from each other in terms of intrinsic activity, receptor site affinity and non-opioid effects.[19]

Indications for starting with an alternative opioid other than morphine include:
- Patient's reluctance to take morphine despite appropriate counselling;
- History of subacute intestinal obstruction – to minimise constipation and reduced gastrointestinal transit time – fentanyl may be the preferred choice;
- Patient's reluctance or inability to take oral medication regularly;
- Significant renal impairment; or
- Severe hepatic impairment.

Opioid rotation
Opioid rotation involves switching from one opioid to another. The clinician should consider opioid rotation when a patient has:[20]
- Difficulty tolerating the initial opioid prescribed due to intolerable side effects (e.g. nausea, pruritus, myoclonus); or
- Poor pain control with the initial opioid, despite appropriate titration

- Worsening of renal or hepatic function.

The initial dose of the second opioid depends on the relative potency of the two drugs. If the patient's pain is well controlled, the equianalgesic dose for the new opioid is calculated then decreased by 25 percent to 50 percent to adjust for incomplete cross-tolerance[20], which is the idea that the new drug may be more effective because of differences in potency or drug bioavailability. Clinical judgement should be used in selecting the appropriate dose, and the patient should be followed up closely as the dose initially chosen may require titration.[12]

Fentanyl
Fentanyl is a strong μ-opioid receptor agonist. It has a relatively low molecular weight and is lipophilic, making it suitable for transdermal (TD) administration. TD fentanyl is contraindicated in patients with acute (short-term) pain and in those who need rapid dose titration for severe uncontrolled pain. TD fentanyl is most appropriate for patients already on a stable dose of morphine (or other opioid analgesic) for ≥1 week.[12]

Indications for using TD fentanyl instead of morphine include:
- Intolerable undesirable effects with morphine (e.g. nausea and vomiting, constipation, hallucinations);
- Renal failure (fentanyl has no active metabolite);
- "Tablet phobia" or poor compliance with oral medication;
- Stable pain and difficulty swallowing; or
- High risk of tablet misuse/diversion.

In Singapore, fentanyl is available in TD and injectable formulations, with TD fentanyl patches available in three strengths: 12, 25 and 50mcg/hour for 3 days. Patches should be applied to dry, non-inflamed, non-irradiated, hairless skin on the upper arm or trunk, and removed after 72 hours, with the new patches applied to a new position so as to rest the underlying skin for 3 to 6 days. Once applied, systemic analgesic concentrations are generally reached within 12 hours, so if converting from:
- 4-hourly oral morphine, give regular doses for the first 12 hours after applying the patch;
- 12-hourly modified release (MR) morphine, apply the patch and the final MR dose at the same time; or
- A syringe driver, continue the infusion for about 8–12 hours after applying the patch.

It is important to give adequate rescue doses of morphine when TD fentanyl is prescribed. Table 3 indicates a safe corresponding starting dose for TD fentanyl for a patient already on morphine, and an appropriate rescue dose. For patients taking a dose of morphine that is not the exact equivalent of a fentanyl patch, it will be necessary to opt for a patch which is either slightly more or slightly less than the morphine dose. Thus, if the patient still has pain, round up to a higher patch strength; if pain-free and frail, round down.[12]

Oxycodone
Oxycodone is a strong opioid with similar properties to

Table 1: Adverse effects of morphine

Adverse effect	Incidence	Dose-related	Tolerance	Comments/Management
Constipation	90%	Partly	No	Regular laxatives
Nausea/vomiting	30–40%	Yes	Yes	Anti-emetics: Metoclopramide 10mg tds prn or Haloperidol 0.5–1mg on prn
Sedation	?20%	Yes	Yes	Usually mild and self-limiting. If persists, reduce dose by 25–50%
Dry mouth	40%	?	?	Good oral care
Confusion	<1%	Yes	No	Reduce dose/switch opioid
Hallucinations	<1%	Yes	No	Reduce dose/switch opioid
Urinary retention	Rare	?	?	Switch opioid
Myoclonus	?5%	Yes	?	Usually occurs with high doses and is a sign of opioid toxicity. Reduce dose/switch opioid

? indicates limited data

Table 2: Common concerns of patients and families about morphine

Common concerns	Explanation
Fear of addiction	When used for pain control, addiction rarely occurs.
Fear of tolerance ("I will need higher and higher doses for morphine to work")	Morphine does not become less effective with time. Doses may increase in the future if symptoms worsen but that is not due to the drug not working anymore.
Fear of using it too early / "saving" it for later use ("If I take morphine now, when my pain gets worse nothing else will work")	There is no maximum dose of morphine as long as there are no intolerable side effects. There are alternative strong opioids if for some reason morphine needs to be discontinued.
Fear of prognosis ("If I take morphine now, it means I'm dying soon")	Pain is not a prognostic factor. Morphine use depends on pain; not severity of illness.
Fear of harm to body ("Morphine is poisonous")	Morphine does not damage internal organs (e.g. liver or kidneys). In fact it is safer compared with analgesics like NSAIDs.
Fear of respiratory depression	When carefully titrated against symptom, morphine does not result in respiratory depression, even in non-malignant conditions such as COPD.

Table 3: Comparative doses of PO morphine and TD fentanyl (based on dose ratio 100:1)[12]

PO Morphine		TD Fentanyl
mg/24h	prn mg[a]	mcg/h
30	5	12
60	10	25
120	20	50
180	30	75
240	40	100

a. *Using traditional 1/6 of total daily dose as prn dose.*

morphine. By mouth, oxycodone is approximately two times more potent than morphine. Oxycodone is available in oral and injectable formulations. Like morphine, oral oxycodone is available in both normal-release (capsules) and modified-release formulations (tablets). Dose reduction is recommended in patients with hepatic or renal impairment. Because oxycodone is more expensive, it should generally be reserved for patients who cannot tolerate morphine.[12]

Hydromorphone

Hydromorphone is an analogue of morphine with similar pharmacokinetic and pharmacodynamic properties. Caution should be exercised in severe hepatic impairment because metabolism may be impaired and result in an increase in plasma hydromorphone concentration. In renal impairment, glucuronide metabolites will accumulate and opioid neurotoxicity has been reported in patients with renal failure taking hydromorphone.

Methadone

Methadone is a unique synthetic opioid agonist with delta receptor affinity, N-methyl-D-aspartate (NMDA) receptor antagonism and monoamine reuptake inhibition. These unique properties make it the opioid of choice for patients with more complex pain syndromes, particularly those with neuropathic pain syndromes. However, the use of methadone in pain management is limited by its pharmacokinetics and pharmacodynamics, specifically its multiple drug interactions, long half-life, and highly variable dose conversion from other opioids. Methadone is metabolised mainly in the liver to several inactive metabolites. About half of the drug and its metabolites are excreted in the intestines and half by the kidneys, most of the latter unchanged. Hence, renal and hepatic impairment do not affect methadone clearance.[12] Due to the complexities in using this medication, it is always best for the novice to perform conversions under the guidance of an expert in the use of methadone.[21]

OPIOID USE IN RENAL AND HEPATIC DYSFUNCTION

Pain management is complicated by altered pharmacokinetics and pharmacodynamics of opioids in patients with renal failure. Regardless of the cause of the renal failure, the effect of decreased kidney function may result in variable metabolism of medications and the presence of pharmacologically active metabolites must be considered when prescribing opioids for these patients. Both the choice and dosage of the opioid must be carefully considered in patients with renal failure, with special attention to accumulation of active and toxic metabolites.[22-23] The liver is the major site for transformation of opioids from parent compounds to active or inactive

APPROXIMATE DOSE CONVERSION RATIOS

Table 4: PO to PO opioid conversion

Conversion	Ratio	Calculation	Example
Codeine to morphine	10:1	Divide 24h codeine dose by 10	PO codeine 240mg/24h → PO morphine 24mg/24h
Tramadol to morphine	5:1	Divide 24h tramadol dose by 5	PO tramadol 300mg/24h → PO morphine 60mg/24h
Morphine to oxycodone	2:1	Divide 24h morphine dose by 2	PO morphine 30mg/24h → PO oxycodone 15mg/24h
Morphine to methadone	Discuss with palliative medicine consultant		

Table 5: PO to IV/SC opioid conversion

Conversion	Ratio	Calculation	Example
Morphine to morphine	3:1	Divide 24h morphine dose by 3	PO morphine 30mg/24h → IV/SC morphine 10mg/24h → IV/SC morphine 0.4mg/hr
Morphine to fentanyl		Use same calculation as for fentanyl patch	

metabolites. In patients with liver failure, reduced metabolism usually results in accumulation of the parent drug in the body with repeated administration. Caution needs to be exercised when using opioids for patients with moderate to severe liver failure, with judicious dose increases and careful monitoring for side effects.

ADJUVANT ANALGESICS

Adjuvant analgesics are usually defined as drugs that are indicated for reasons other than pain (e.g. depression, epilepsy) but are analgesic in specific circumstances. In the context of advanced illness, an adjuvant analgesic drug is most often considered when a patient has opioid-refractory neuropathic pain, bone pain, or pain related to bowel obstruction.[5] As a general rule, a trial of an adjuvant analgesic in the setting of poor opioid responsiveness should usually be considered only after efforts have been made to optimise opioid therapy, to ensure that the second drug is needed, reduces the risk of additive toxicity by eliminating the need to titrate both drugs simultaneously, and limits confusion in determining the source of an adverse drug effect should one arise.[28]

Table 6: Recommended use of selected opioids in patients with renal dysfunction[24-25]

Opioid	Recommended Use	Comment
Morphine	Use cautiously; adjust dose as appropriate	Metabolites can accumulate causing increased therapeutic and adverse effects
Hydromorphone	Use cautiously; adjust dose as appropriate	The 3-glucuronide metabolite can accumulate and cause neuro-excitatory effects
Oxycodone	Use cautiously with careful monitoring; adjust dose if necessary	Metabolites and parent drug can accumulate causing toxic and CNS-depressant effects
Codeine	Do not use	Metabolites can accumulate causing adverse effects
Methadone*	Appears safe	Metabolites are inactive
Fentanyl*	Appears safe; however, a dose reduction may be necessary**	No active metabolites and appears to have no added risk of adverse effects; monitor with long term use

Negligible or no active metabolites; although, not considered first-line therapy.

Table 7: Recommended use of opioids in hepatic dysfunction [26-27]

Opioid	Recommended usage	Comment	Dosing recommendations*
Morphine	Use cautiously and monitor patient for sedation.	In severe hepatic impairment, the parent drug may not be readily converted to metabolites.	Increase the dosing interval by twice the usual time period.
Hydromorphone	Use cautiously and monitor patient carefully for symptoms of opioid overdose.	In severe hepatic impairment, the parent drug may not be readily converted to inactive metabolites.	Decrease initial dose by 50% of the usual amount.
Oxycodone	Use cautiously and monitor patient carefully for symptoms of opioid overdose.	In severe hepatic impairment, the parent drug may not be readily converted to inactive metabolites.	Decrease initial dose by 1/2 to 1/3 of the usual amount.
Codeine	Avoid use.	In severe hepatic impairment, codeine may not be converted to	-
Methadone	Not advised	Not advised in severe liver failure due to risk of methadone accumulation	-
Fentanyl	Appears safe, generally no dose adjustment necessary.	Decreased hepatic blood flow affects metabolism more than hepatic failure	Dosing adjustment usually not needed.

Recommended dose in severe hepatic impairment.

Glucocorticoids

In palliative care, glucocorticoids are often used to alleviate symptoms such as pain, nausea and fatigue. A large body of clinical experience suggests that glucocorticoids may be beneficial for a variety of types of pain, including neuropathic and bone pain, pain associated with capsular expansion, pain from bowel obstruction, pain caused by lymphoedema, and headache caused by raised intracranial pressure. Dexamethasone is usually the preferred glucocorticoid for the management of pain, due to its long half-life and relatively low mineralocorticoid effects. In the setting of advanced illness, the risk of long-term toxicity, including myopathy, immunocompromise, psychomimetic effects and hypoadrenalism, is attenuated by limited life expectancy and the need to address the multiple sources of suffering.[28]

Antidepressants

In opioid-treated populations with advanced medical illness, antidepressants have been predominantly used for neuropathic pain. The best efficacy has been established for tricyclic antidepressants (TCAs) (e.g. amitriptyline and nortriptyline), and the serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g. venlafaxine and duloxetine). Tricyclic Antidepressants are relatively contraindicated in patients with serious heart disease, severe prostatic hypertrophy and narrow-angle glaucoma.

Anticonvulsants

Gabapentin and pregabalin have been extensively studied in diverse types of neuropathic pain, particularly post-herpetic neuralgia and painful diabetic neuropathy. Fewer data are available in patients with neuropathic pain related to cancer or its treatment, although they are widely used. Both drugs are not metabolised by the liver and have no known drug-drug interactions. Both are excreted by the kidneys, which necessitates dose reduction in the setting of renal impairment. Their main side effects are mental clouding, dizziness, and somnolence.

OTHER TREATMENT MODALITIES FOR PAIN MANAGEMENT

Although systemic pharmacotherapy is the mainstay of treatment for patients with pain related to advanced illness, other modalities of treatment can be extremely valuable for pain control, especially in patients with refractory pain or intolerance to systemic opioids.

Radiotherapy

Radiotherapy is highly effective in palliating symptoms of cancer including pain, with an 80 to 90 percent response rate, with minimal side effects. It can provide prompt, effective and durable pain relief. Short courses (1 to 5 fractions) of radiation compared to longer course radiation gives equal relief from pain, can increase the speed of pain relief and decrease the patient's burden of having to travel to the radiation centre.[29]

Radiopharmaceuticals

Radionuclides such as radioactive strontium and samarium are highly effective in the control of bone pain in selected patients. The most appropriate patients for radiopharmaceuticals are those with epithelial cancers such as prostate and breast cancer, multiple sites of disease but predominantly in the bone, a positive technetium-99 bone scan, a life expectancy longer than 3 months, and good bone marrow reserve. Radiopharmaceuticals are expensive, however they are

Table 8: Adjuvant analgesics* [4]

Class	Main indications	Mechanism(s) of action	Examples	Typical regimen	Undesirable effects
Corticosteroids	Nerve compression Spinal cord compression	Reduce peri-tumour oedema	Prednisolone Dexamethasone	15-30mg om 8-16mg om	Hyperglycaemia, anxiety, steroid psychosis, myopathy
Antidepressants	Nerve injury pain	Potentiation of two spinal descending inhibitory pathways	Amitriptyline Nortriptyline	25-100mg on	Antimuscarinic effects, drowsiness, postural hypotension (particularly amitriptyline)
Anti-epileptics	Nerve injury pain	Potentiation of GABA inhibitory & glutamate excitatory mechanisms in dorsal horn Selective calcium-channel blockade	Sodium valproate Gabapentin	400-1000mg on 100-300mg tds	Drowsiness Drowsiness
NMDA receptor channel blockers	Pain poorly responsive to analgesic	Block channel in NMDA-type glutamate receptor channel	Ketamine	100-500mg/24 SC 10-20mg q6h PO	Dysphoria
Antispasmodics	Bowel colic	Relax intestinal smooth muscle	Hyoscine butylbromide	60-160mg/24h SC	Peripheral antimuscarinic effects
Muscle relaxants	Muscle spasm	Relax somatic muscle	Baclofen	10mg tds	Drowsiness, ataxia
Bisphosphonates	Intractable metastatic bone pain	Block osteoclast activity	Pamidronate Zoledronic acid	90mg IV every 4 weeks 4mg IV every 4-8 weeks	Pyrexia, flu-like malaise for 1-2 days (uncommon for zoledronic acid)

Choice of drugs and dose varies widely, particularly for adjuvant analgesics for neuropathic pain.

considered cost-effective because the associated reduced analgesic and hospital use may offset the cost of the radionuclide.[30]

Nerve blocks

Nerve blocks have a strong clinical record of pain relief, allowing better pain management and reduction in drug side effects. In general, 50 to 90 percent of patients have substantial relief of pain from a nerve block that is evident immediately, with no major side effects. Some common situations in which nerve blocks may significantly improve pain management include the abdominal pain of pancreatic cancer and localised "plexopathy" pain from damage to a group of nerves such as the brachial plexus under the shoulder.[31]

Neuraxial infusion

Neuraxial infusion refers to the intervention by which one or more drugs are infused into the epidural or intrathecal (subarachnoid) space. Most patients achieve acceptable pain relief with oral medications, but some have intractable pain or side effects despite appropriate therapy. For this group of patients, epidural or intrathecal therapy is an important proven option that offers the advantages of superior pain relief, fewer systemic side effects, and the ability to use different classes of medications such as local anaesthetics, for which there is no oral equivalent.[32]

Psychological, rehabilitative and integrative therapies

Poorly controlled pain can affect the psychological, cognitive, social, and spiritual domains of patients' lives, with a profoundly negative impact on quality of life not just for the patients but the caregivers as well. Outcomes related to the pain, and to pain-related impairment of mood and function may be enhanced by the adjunctive use of non-invasive psychological, rehabilitative and integrative therapies, using a multidisciplinary approach. Such strategies may provide satisfactory pain relief with fewer drug side effects, and/or better outcomes with regard to physical and psychosocial functioning.

CONCLUSION

Pain is a highly prevalent but frequently undertreated symptom at the end of life. Pharmacological therapy is the mainstay of pain management in patients with advanced illnesses. With the appropriate use of pharmacological agents & other approaches, good pain control can be achieved in the majority of patients. The general principles of good pain management include a comprehensive initial pain assessment, appropriate prescription and escalation of analgesic medication with round-the-clock administration, frequent reassessment for efficacy and side effects of treatment, and assessing the impact of pain on the patient's and family's psychological, social and spiritual well-being, and overall quality of life.

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LEARNING POINTS

- **Pain is a highly prevalent symptom in patients with advanced illnesses.**
- **Pharmacological therapy is the mainstay of pain management at the end of life.**
- **The general principles of good pain management include a comprehensive initial pain assessment and frequent reassessment for efficacy and side effects of treatment.**
- **Good pain control can be achieved in the majority of patients when well-established treatment guidelines are followed.**