An Indian Primer of Palliative Care
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For medical students and doctors

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Chennayya, a 50 year-old man, was diagnosed with cancer of the buccal mucosa. He attended a busy outpatient clinic with persistent pain over the jaw. It has become more severe in the last 2 weeks. He has not had any relief with the medications prescribed by his primary care doctor. He has foul-smelling wound over the jaw and has not slept well for several weeks due to pain. He is a carpenter and is now unable to work due to illness.

**What is the impact of severe persistent pain on Chennaya’s life?**

**How will you approach the total pain reflected in his eyes?**

By the end of the chapter, the student should be able to:

1. Differentiate between acute and chronic/persistent pain.
3. Recognize pain relief as an important aspect of quality of care.
4. Describe pathophysiology and impact of persistent pain.
5. Describe the drugs in the WHO analgesic ladder and their effective usage.
What is Pain?

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

International Association for Study of Pain (IASP)

Pain is a common accompaniment of many chronic diseases, for example approximately 30-50% of people with cancer experience pain during treatment and 70-90% of people with advanced cancer experience pain (Portenoy RK).

Pain is what the patient says hurts; when he or she says it does; Believe the patient regarding his or her pain.

Free nerve endings of Aδ and C fibres are stimulated through the release of chemical mediators at the site of pathology and the signals travel along the peripheral nerve up to the dorsal horn of the spinal cord. It ascends along the contra-lateral spino-thalamic tract to reach the thalamus and eventually the sensory cortex.

Pain is not just a sensation or information appraisal; it is an emotional experience

People do not experience pain in their nerve endings but in their minds - where life events and memories combine with physical stimuli to create suffering or resilience. Suffering is very particular to each individual. The anguish of physical pain may be made worse by psychological, social, or spiritual factors (Hayden, 2006).

Chennayya has persistent, unremitting pain over his jaw; this is the physical component of pain. He is anxious and depressed due to his disease and the pain. This is the psychological aspect of his pain. Each worsens the other. The net result is his “pain experience.”

Until recently he was the breadwinner of the house, caring for his family. Now, he is no longer contributes economically to his family. He is dependent and feels desolate. Moreover since there is a foul smell emanating from his wound, he shuns company and friends, and does not leave the house. He feels isolated. This is the social component of pain.

He is only 50 years old. He wonders why God did this to him. He had the habit of betel chewing which he had discontinued after the carcinoma was diagnosed. It is possible that he may be harbouring guilt that his present illness is the result of his habit? This question of “Why me?” or “Is this a punishment from God?” could be understood as the spiritual component of pain.
Evaluation of pain

Why is it that the pain medication has not given him relief to the extent he is unable to sleep for the past several weeks? Has his pain been properly evaluated?

Total pain is “the suffering that encompasses all of a person’s physical, psychological, social, spiritual and practical struggles.”
Let us consider Chennayya’s pain history:

Is his pain acute or chronic?
What is the severity of pain?

<table>
<thead>
<tr>
<th>Acute pain</th>
<th>Chronic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicates potential or actual tissue injury</td>
<td>Multi-factorial with neuro-chemical changes</td>
</tr>
<tr>
<td>Autonomic responses more dominant</td>
<td>Autonomic responses settle and the vegetative responses more dominant</td>
</tr>
<tr>
<td>Self-limiting</td>
<td>Unremitting, progressive</td>
</tr>
<tr>
<td>Intensity reduces as healing progresses</td>
<td>Constant reminder of a life-threatening disease</td>
</tr>
<tr>
<td>Plays a protective role</td>
<td>Chronic pain takes on characteristics of a disease</td>
</tr>
</tbody>
</table>

Chennayya had pain for two years, which had led to diagnosis of the carcinoma of buccal mucosa. His pain is persistent and should be acknowledged as such. Often we disregard chronic or persistent pain as mild, since the patient does not fit with the image that we have of a person in pain (crying or shouting in pain).

When pain persists, what happens to the intensity of its experience? Does it stay same or does it increase or decrease over time?

In acute pain situations, the sensation of pain acts as a warning of actual or potential injury. Persistent pain is more than just an extension of acute pain over prolonged periods. Changes occur within the pain pathways that augment the frequency and the intensity of impulses reaching the central nervous system. The emotional consequences are also worse in long-standing pain.

What is the pathophysiology of chronic or persistent pain?
- Pain receptors do not adapt over time. They continue to sense noxious stimuli.
- With persistent pain:
  - There is further sensitisation of active nociceptors. Neurochemicals such as prostaglandins, potassium, and bradykinin accumulate and sensitise the nociceptors so that successive stimuli cause progressively increasing nociception.
  - Silent (sleepy) nociceptors are recruited, which increases the intensity of pain.
  - The intensity is also amplified by sensitisation of dorsal horn cells-the “wind-up” phenomenon via N-methyl-D aspartate (NMDA) receptors.
  - Gradually the adjacent spinal segments are also recruited into the firing of signals and this widens the painful area.
• Persistent reflex muscular response to pain causes areas of sustained muscular contraction (myofascial trigger points), which may cause additional pain.
• Reflex vasoconstriction in the area of pain can worsen ischaemic pain.
• The inhibitory descending inputs from brainstem get over-whelmed and become ineffective over time.

End result: Worsening of pain in intensity, severity and extent with time.

In a patient with cancer or other major diagnosis, cancer may not be the only cause for pain. Chronic pain may have several contributors. Let us consider another clinical scenario to understand this:

Ramani is a 35 year old woman with HIV with painful lesions in the face and neck. This pain is disease-related. Subsequently, as a result of treatment, she developed neuropathy. This new pain is treatment-related. After a few days, she reports with painful dysphagia and is found to have candidiasis. This pain is a result of her debility and poor immunity. A new pain may develop at anytime if she develops infection or ulcerations at any site. This would be pain due to co-morbidity.

Table 3.1 – In chronic disease, not all pain is related to the disease.

<table>
<thead>
<tr>
<th>Disease related</th>
<th>Treatment related</th>
<th>Debility related</th>
<th>Co-morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue infiltration</td>
<td>Surgery</td>
<td>Constipation</td>
<td>Spondylitis</td>
</tr>
<tr>
<td>Visceral/nerve compression</td>
<td>Post operative care</td>
<td>Deep vein thrombosis</td>
<td>Migraine</td>
</tr>
<tr>
<td>Nerve infiltration</td>
<td>Scars</td>
<td>Pressure sores</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Spread to bone</td>
<td>Adhesions</td>
<td>Catheter sepsis</td>
<td>Infections</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>Radiotherapy dermatitis</td>
<td>Bladder spasm</td>
<td>Angina</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>Fibrosis</td>
<td>Aspiration pneumonitis</td>
<td>Trauma</td>
</tr>
<tr>
<td>Raised intra cranial pressure</td>
<td>Chemotherapy</td>
<td>Stiff joints</td>
<td>Acid peptic disease</td>
</tr>
<tr>
<td>Stricture of hollow viscus</td>
<td>Neuropathy</td>
<td>Post-herpetic neuralgia</td>
<td>Glaucoma</td>
</tr>
</tbody>
</table>

Different types of pain and their temporal relation
1. Baseline pain – may be continuous or intermittent.
2. Breakthrough pain- often high intensity. It comes on predictably with weight bearing, movement, or change of dressing; OR it occurs spontaneously without warning such as
colic, or shooting pain. The breakthrough pain lasts between few seconds to 30 minutes.

3. Incidental pain - associated with precipitating factor such as movement.

4. “End of dose” pain - occurs prior to the next scheduled dose and is gradual in onset and lasts until the pain medicine is dosed again.

**What is the pathological type of Chennayya’s pain?**

**Why should we differentiate the two types of pain?**

We should differentiate the two types of pain because the choice of medications and the management varies.

![Diagram](image)

**Fig 3.2 - Diagrammatic representation of types of pain**

<table>
<thead>
<tr>
<th>Features</th>
<th>Nociceptive pain</th>
<th>Neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Stimulation of nociceptors (free nerve endings) in visceral or somatic structures</td>
<td>Abnormal impulse generation in peripheral nerve, spinal cord and brain</td>
</tr>
<tr>
<td>Localisation</td>
<td>Localized in somatic, diffuse in visceral pain</td>
<td>Neuro-dermatomal distribution</td>
</tr>
<tr>
<td>Quality</td>
<td>Throbbing, aching, gnawing</td>
<td>Burning, lancinating, shooting, stabbing, pricking etc</td>
</tr>
<tr>
<td>Abnormal sensation</td>
<td>None</td>
<td>Allodynia, hyperalgesia</td>
</tr>
</tbody>
</table>

**Now what is your assessment of Chennayya’s pain?**

Chennayya has persistent pain over the jaw, which is gripping in character and is almost always present. Apart from that, he also has transient intermittent shooting pain radiating down from the jaw up to the ear. He has a burning sensation in the lower part of his jaw. He describes the persistent pain as having a score of 6/10 in intensity and the shooting pain as 10/10, very severe, spontaneous and unpredictable.

Thus he has both types of pain:

- nociceptive pain, the background continuous pain.
• intermittent neuropathic pain with a shooting and burning component.
• breakthrough/ incident pain provoked by chewing and swallowing.

All of these components need to be considered when deciding on a treatment plan.

**Allodynia and Hyperalgesia**

Ms. Hema has severe lymphedema following modified radical mastectomy and in addition, now has recurrence with possible infiltration in her brachial plexus. She has severe pain on touch and cannot bear it when the fabric of her clothes rubs against her skin.

A stimulus which ordinarily does not cause pain, such as light touch, is called allodynia.

Pressure on her edematous arm causes excruciating pain. An exaggerated pain response to a painful stimulus is called hyperalgesia.

Always listen carefully to the patient regarding his/her pain
The details of pain assessment can be memorised using the mnemonic “PQRST”

P - Palliative/ provocative factors
Q - Quality of pain (nature of pain; e.g. burning, aching)
R - Radiation of pain
S - Site, Severity
T - Temporal factors (duration, diurnal variation of pain, continuous or intermittent)

In addition, always evaluate: how is the pain affecting the person?
Assessment of Pain

This may be done using various pain scales available. The commonly used ones are:

1. Categorical pain scale: Patient is asked to grade his pain as having “no pain, mild pain, moderate pain, severe and excruciating pain.”
2. Numerical Rating Scale (NRS):

   ![Numerical Rating Scale](image)

   It is explained to the patient that zero represents “no pain” and 10 represents the “worst imaginable pain”. Then, the patient is asked to score his pain on this scale according to the severity.

3. Visual Analogue Scale (VAS):

   ![Visual Analogue Scale](image)

   One side of VAS has no markings except the two extreme points. The other side has marks from zero to 100. The unmarked side is shown to the patient who is asked to mark the pain according to the severity. Then the assessor will view the pain on a 0-100 scale on the reverse side.

4. Non-verbal rating scale (Wong-Baker Faces Scale) - usually used to assess pain in children.

   ![Wong-Baker Faces Scale](image)

   Pain scores of 0-1 may be considered MILD PAIN.
   Pain score of 2-3 may be considered MODERATE PAIN.
   Pain score of 4-5 may be considered SEVERE PAIN.
   The aim of pain management is to keep the pain score at a level that the patient considers satisfactory.
Location:

Many patients have more than one pain. Two pains may be of different types and of different etiology. It is important to document them so that we can monitor progress. The site of each pain is marked on a body chart.

Meaning:

Assessment of pain is not complete without going into the impact of the pain on the person. What is the meaning of the pain for Chennayya? Does he see it as punishment for his sins? Does he read impending death in it? Is he feeling guilty that the whole family is troubled because of his pain?

Meaning of the pain - The meaning that the patient may attribute to the suffering is very significant. It is important to know what the patient thinks about the pain experience; his/her understanding of the cause and reason for the pain, as well as how it affects him/her as a person. This aspect needs to be acknowledged and addressed within the therapeutic plan.
Test your knowledge

1. Which of the following statements is TRUE regarding chronic pain?
   a. Chronic pain is essentially protective.
   b. Chronic pain is limited to the area of injury.
   c. Nociceptors get desensitized with repeated stimuli.
   d. There is ‘wind-up’ phenomenon in chronic pain conditions.

2. Which of the following is TRUE about severe cancer pain?
   a. It is a part of healing process.
   b. Most cancer pain responds to WHO analgesic ladder.
   c. Cancer pain is always nociceptive.
   d. The pain experience decreases as time passes.

3. Painful response to a non-painful stimulus is called:
   a. Allodynia
   b. Hyperalgesia
   c. Hyperaesthesia
   d. Akathisia

4. Which of the following is an example of visceral pain?
   a. Pain due to skeletal metastasis
   b. Pain due to skeletal muscle spasm
   c. Pain due to liver capsule stretch
   d. Sciatica

Answer Key:
1 – d; 2 – b; 3 – a; 4 – c
Management of pain

Up to 71-76% of patients with cancer-related pains can have satisfactory relief by following the guidelines of the WHO analgesic ladder.

Fig 3.3 - WHO Analgesic ladder

Table 3.3 - Principles of WHO analgesic ladder use:

<table>
<thead>
<tr>
<th>By the clock</th>
<th>Continuous pain needs continuous relief. Prescribe drugs according to their duration of action; not arbitrarily or on as-needed basis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>By the mouth</td>
<td>Give medicines orally as much as possible. This is the simplest route. A well-informed patient can use the oral medications by himself. Injections require professional help, are a source of pain by themselves, and are best avoided.</td>
</tr>
<tr>
<td>By the ladder</td>
<td>Choose medications from the WHO ladder, according to severity of pain, but with flexibility. In severe pain, it is permissible to start at step III.</td>
</tr>
<tr>
<td>Individualised approach</td>
<td>Prescription should mention dose for breakthrough pain. This improves the effectiveness, level of control and helps to fine tune the dose. Choose the right drugs, routes and dosages based on co-morbidities, drug interactions and side effect profile for that patient. In short, each person should be assessed in detail physically and holistically and managed accordingly.</td>
</tr>
</tbody>
</table>
### Table 3.4 - Drugs in WHO Analgesic ladder

<table>
<thead>
<tr>
<th>Non-Opioids</th>
<th>Opioids for mild to moderate pain</th>
<th>Opioids for moderate to severe pain</th>
<th>Adjuvant analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>paracetamol</td>
<td>codeine</td>
<td>morphine</td>
<td>tricyclic</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>tramadol</td>
<td>fentanyl</td>
<td>antidepressants</td>
</tr>
<tr>
<td>diclofenac</td>
<td>tapentadol</td>
<td>methadone</td>
<td>(amitriptyline,</td>
</tr>
<tr>
<td>naproxen</td>
<td></td>
<td>(not yet sold in India for pain</td>
<td>imipramine)</td>
</tr>
<tr>
<td>indomethacin</td>
<td></td>
<td>relief)</td>
<td>anticonvulsants</td>
</tr>
<tr>
<td>ketorolac</td>
<td></td>
<td></td>
<td>(carbamazepine,</td>
</tr>
<tr>
<td>etoricoxib</td>
<td></td>
<td></td>
<td>valproate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>gabapentin,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pregabalin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anticholinergic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(hyoscine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Muscle relaxants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(diazepam)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>blocker ketamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bisphosphonates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Local anesthetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>
Step 1 Drugs from the WHO Analgesic Ladder

Non-opioid analgesics

These include paracetamol and a broad class of drugs, the non-steroidal anti-inflammatory drugs (NSAIDs). Sometimes paracetamol is included amongst NSAIDs, but it is very different in its analgesic mechanism and can be safely combined with other NSAIDs.

Paracetamol is an analgesic with good safety margin; it is a good analgesic for its additive effect. It is usually given 6 hourly to maximum of 4g per day. In those with liver dysfunction, it is used with caution. Unlike the NSAIDs, it has a predominant central action.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs exert anti-inflammatory action by inhibiting prostaglandin synthesis through the cyclo-oxygenase (COX) pathways and hence are very effective in nociceptive pain associated with inflammation. NSAIDs may be useful in neuropathic pain also if there is associated nociceptive component (mixed pain) or if the neuropathic pain is associated with a process of inflammation as in malignancy or acute injury. It is unlikely to be helpful where the neuropathic pain does not have an inflammatory component as in post-herpetic neuralgia.

NSAIDs can be divided into following groups.

- Non-selective NSAIDs: These inhibit both COX-1 and COX-2 enzymes. These have more gastrointestinal side effects than selective COX-2 inhibitors and have the potential to worsen bleeding.
- COX-2 selective NSAIDs: They selectively inhibit COX-2 enzymes. These have less gastrointestinal side effects. They do not inhibit platelets and so would be safe in presence of bleeding tendency. On the other hand, they may have a pro-thrombotic effect and so may be associated with increased cardiovascular and cerebrovascular incidents. They are specially indicated for short-term use when bleeding or gastritis is a particular concern.

It is important to remember that both selective and non-selective NSAIDs can cause renal dysfunction in presence of hypovolemia or in pre-existing kidney disease. The potentially diminished renal function may also predispose to water retention thereby worsening hypertension or heart failure.

There is recent evidence that diclofenac may be significantly COX-2 selective and so carries the risk of adverse coronary or cerebral events in long term use.13 Ibuprofen and naproxen were shown to be the safest in coronary and cerebral events. However, their relative safety is valid only if the dose is restricted as shown in the table below.

Renal failure, hypertension and possibility of congestive cardiac failure have to be monitored for all patients on NSAIDs regardless of COX selectivity.

---

1. Fosbol E.L et al; Circulation; Circ Cardiovasc Qual Outcomes 2010;3;395–405
Table 3.5 - Examples of Non-selective COX inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
<td>TDS or QDS</td>
<td>PO</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250-500 mg</td>
<td>BD</td>
<td>PO, suppository</td>
</tr>
</tbody>
</table>

An increased risk of thrombotic events leading to myocardial ischemia and cerebrovascular events has been found for COX-2-selective inhibitors. The risk of such events increases with higher doses and prolonged treatment.

Table 3.6 - Risk factors for specific toxicity with NSAIDs

<table>
<thead>
<tr>
<th>Risk factors for GI toxicity</th>
<th>Risk factors for renal toxicity</th>
<th>Risk factors for pro-thrombotic action</th>
</tr>
</thead>
<tbody>
<tr>
<td>High NSAID dose</td>
<td>Advanced age</td>
<td>Use of COX-2 drugs</td>
</tr>
<tr>
<td>History of upper GI symptoms</td>
<td>Poorly controlled diabetes</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Advanced age</td>
<td>Dehydration</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Concurrent aspirin or corticosteroid use</td>
<td>Concurrent nephrotoxic</td>
<td>Hyperlipidaemia</td>
</tr>
<tr>
<td>Comorbidities (e.g rheumatoid arthritis)</td>
<td>Dyes used in imaging.</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Poor kidney perfusion.</td>
<td>Smoking</td>
</tr>
</tbody>
</table>
Recommendations for safe prescription of NSAIDs

1. Drugs are to be given by mouth, by the clock, by the ladder for effective and sustained pain relief.
2. Use the lowest possible effective dose for the required duration of treatment.
3. Elderly patients, smokers, alcoholics, those using steroids or aspirin concurrently, or those with a past history of peptic ulceration, GI bleeding or gastroduodenal perforation are more at risk for adverse effects from NSAIDs.
   - A proton pump inhibitor such as omeprazole 20 mg a day on empty stomach is recommended for gastroprophylaxis in high risk patients (age > 65, high-dose NSAID, concurrent steroids or anticoagulant, less than one month of NSAID treatment, debility, prior NSAID-induced ulcer).
   - They are to be avoided in presence of dehydration, gastroenteritis, diuretics, or diabetes.
   - Special caution is advised with concurrent use of nephrotoxic drugs such as contrast agents for radiology procedures.
   - Special caution is advised in patients with possible coronary artery disease, hypertension, asthma, hyperlipidemia, diabetes, renal dysfunction and smokers.
   - COX-2 selective inhibitors are contraindicated in patients with atherosclerotic disease, ischaemic heart disease, cerebrovascular disease or peripheral arterial disease

Long term NSAIDs should be used with caution and with periodic monitoring of renal function.
Test your knowledge

Choose the more appropriate group of non-opioid step I analgesic in following situations.

1. Mr. M., a 66-year-old with diabetes and hypertension
2. Ms. K., a 32-year-old with a history of peptic ulcer disease
3. Mr. L, a 50-year-old with diabetes for 20 years and a serum creatinine of 2.8 mg%
4. Mr. G., a 57-year-old with bleeding polyps
Adjuvant Group of Drugs in Step 1 of the WHO Ladder

The term “adjuvant analgesic” is used for a drug that has a primary indication other than pain but is active also for pain. Adjuvants may be used alone or may be used in combination with a primary analgesic such as NSAID or opioids. They may be classified as:

- Those that improve pain from a specific etiology e.g. tricyclic antidepressants for neuropathic pain or antispasmodics for intestinal colic
- Those improving co-existing conditions thereby contributing to therapeutic response to analgesics e.g. antibiotics when infection is present; bisphosphonates for bone pain

Sometimes, the term “adjuvant” is also used to include those that counter side effects of analgesic drugs e.g. anti-emetics, laxatives.

Table 3.7 – Indications for Adjuvant drugs in pain management

<table>
<thead>
<tr>
<th>Adjuvant Drug</th>
<th>Situation where it may be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Pain caused by inflammation or by elevated intracranial pressure</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Neuropathic pain</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>For colic from tubular structures.</td>
</tr>
<tr>
<td>Antidepressants in regular dose</td>
<td>Clinical depression is contributing to the pain</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Pain related to infection</td>
</tr>
<tr>
<td>Night sedatives</td>
<td>Lack of sleep is lowering pain threshold</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>Anxiety is aggravating the pain</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>For colic from tubular structures.</td>
</tr>
</tbody>
</table>
Management of Neuropathic Pain:

This type of pain often requires the use of adjuvants from the WHO ladder besides the regular analgesics. The following steps may be considered as a general approach to managing neuropathic pain.

![Diagram showing steps for managing neuropathic pain]

Fig 3.4 – Approach to choosing adjuvants other than corticosteroids for managing neuropathic pain. In presence of significant inflammation contributing to nerve compression or of elevated intracranial tension, corticosteroids may be indicated.

Table 3.8– Common medications used in Neuropathic Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>S. Effects &amp; Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Start with 12.5 to 25 mg HS, increase 12.5 to 25 mg every 3-5 days, up to 100 mg/day</td>
<td>Early morning sedation, anti-muscarinic side effects</td>
</tr>
<tr>
<td>Imipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30-60 mg /day HS</td>
<td>Nausea, dizziness, dry mouth, sleepiness</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Valproate</td>
<td>Start with 200mg at bedtime, titrate up by 200 mg every 3-5 days, up to 1 G/day</td>
<td>Gastrointestinal upset, drowsiness, tremor, ataxia</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Start with 50-100 mg TDS, increase every 2 weeks by 200 mg, up to 1G/day</td>
<td>Ataxia, diplopia, nystagmus, blood dyscrasias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Details</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Start with 100 mg TDS, increase 300 mg TDS every week up to 900 mg TDS</td>
<td>Drowsiness, peripheral oedema.</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Start with 75 mg HS and gradually increase to BD or TDS dosage. Max 600 mg/day</td>
<td>Dizziness, sleep disturbances, ataxia, mood disturbances, dry mouth, constipation.</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.2-0.5 mg/kg bodyweight/ dose TDS –QDS PO (sub- anaesthetic dose). Also as continuous subcutaneous infusion at 50-100mg/day; Maximum dose – 200mg / day</td>
<td>Dysphoria, hallucinations, nausea and vomiting, dizziness.</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>1-2 mg/kg over 20 minutes followed by 1-2 mg/kg over 60 minutes (dose could be repeated every 24 hours or may be changed to a continuous infusion)</td>
<td>Serious toxicity is rare at these doses, however, patient should be monitored for signs of mild toxicity: tinnitus, perioral numbness, headache, metallic taste, or drowsiness, and the infusion may be slowed if symptoms become significant. Slowing of the heart rate is common, but bradycardia is rare.</td>
</tr>
</tbody>
</table>

What are the important non-drug treatments for pain relief?

- Empathy, counseling and therapeutic relationship is essential to address the subjective emotional component of the pain experience.
- Physical therapies – heat, transcutaneous electrical nerve stimulation (TENS), ultrasound and exercise
- Radiation therapy for bony pain
- Injection of trigger points with local anaesthetic agent
- Local anaesthetic and neurolytic blocks (e.g. nerve destruction with alcohol or phenol-in-glycerol)
In some centres, nerve blocks are gradually being replaced by epidural or intrathecal analgesia with a continuous infusion of local anesthetic agents with or without opioid analgesics.

- Modification of the patient’s living environment or use of assistive devices (ramps, toilet risers, walkers, wheelchairs).
- Complimentary therapies including yoga, acupuncture and cognitive behavioral therapy (CBT) in improving pain-related behavior and perceived self-efficacy.
- Involvement in activities that bring in joy to the individual’s daily life helps in moving beyond the constant presence that pain has in a person’s life.

Test your knowledge

1. In the WHO analgesic ladder, non-opioid analgesics are:
   a. Used only in step 1
   b. Used in all the 3 steps
   c. Not used with strong opioids
   d. Avoided with adjuvants

2. Which of the following is NOT an adjuvant?
   a. Bisacodyl
   b. Codeine
   c. Amitriptyline
   d. Ondansetron

Answers: 1 – b; 2 – b
Opioids – the Step 2 and Step 3 drugs of the WHO Ladder

Opioid analgesics include naturally occurring, semi-synthetic and synthetic drugs. They combine with opioid receptors (mu, kappa and delta), in the central as well as peripheral nervous system, to produce analgesic action.

**STEP 2 of the WHO Analgesic Ladder**

Step 1 drugs ± weak opioids used in pain of moderate intensity.

*If step 1 medications are not satisfactory for the pain relief, proceed to step 2 of the analgesic ladder as listed above.*

Step 2 medications are not classed as “controlled drugs,” so they are more widely available. One may begin directly at step 2 if the pain is moderate in intensity. Adjuvants are to be added if indicated for specific reasons, as in step 1.

If step 2 medications are not adequate, proceed to step 3. It is conventional to wait for 2 days before climbing up the ladder, but in case of severe pain, the switch to step 3 can be earlier.

**DEXTROPROPOXEPHENE**

Dextropropoxephene was available commercially in combination with Paracetamol. The usual daily dose of Dextropropoxephene is one capsule of 65mg six hourly, which comes to a total daily dose of 260mg of Dextropropoxephene. The drug takes up to 72 hours to reach steady state level. Currently its sale is suspended due to concerns regarding safety and efficacy. Palliative care professionals have appealed to the Government of India against this suspension.

**TRAMADOL**

In addition to being a weak mu receptor agonist, tramadol inhibits the reuptake of serotonin and norepinephrine in the inhibitory pain pathways. It is rapidly absorbed after oral doses and is metabolized in the liver. Analgesia begins within one hour and starts to peak in two hours. It is usually used in doses of 50-100 mg Q6-8 H up to a maximum of 400 mg/ day. It shares all the opioid side effects of the class like nausea, vomiting, constipation, neuropsychiatric symptoms, and pruritus. It also reduces seizure threshold.

**TAPENTADOL**

This is a relatively new drug. This too is a mu receptor agonist which also inhibits the reuptake of serotonin and nor-epinephrine in the inhibitory pain pathways. It seems to have a better side effect profile than tramadol, but it still has the potential to contribute to/precipitate serotonin syndrome and to induce physical/psychological dependence. It is usually used in doses of 50-150 mg Q6-8 hours up to maximum of 400 mg/ day.

**BUPRENORPHINE**

Buprenorphine is a partial agonist at mu receptor and antagonist at kappa and delta receptors. Buprenorphine is used for moderate to severe cancer and non-cancer pain, however it is NOT a preferred drug in cancer pain due to ceiling effect. There is a limit to analgesia that can be

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achieved without significant side effects or toxicity. Buprenorphine has poor oral bioavailability and is available as sublingual, transdermal and parenteral preparations.

**Step 3 medications of WHO Analgesic Ladder**

Step 3 medicines are used when step 2 medicines are inadequate or when pain is excruciating at the onset. Step 1 medicines are continued along with step 3 opioids.

**MORPHINE**

*Oral morphine is the gold standard for treatment of cancer pain.*

It is available as injections, tablets and suppositories. In addition to the oral route, morphine may be used through parenteral, rectal, topical and neuraxial route. IM administration is least preferred due to erratic absorption, difficulty in assessing response and thus possibility of overdose. This is also an additional cause for pain.

It acts mainly on the mu receptor. It is metabolized mostly in the liver and converted into two major metabolites namely morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G). M6G is the active component which significantly contributes to pain relief and M3G is believed to produce CNS adverse effects like myoclonus, dysphoria and delirium.

Administered orally, morphine will take about 24-36 hours to achieve steady state level in the blood. If at the end of 36 hours or so, pain relief lasts for less than 4 hours or the patient has to take two or more PRN doses, the 4 hourly dose should be increased by 50% and thereafter reviewed every two days.

**Comparison of step 2 opioids with morphine**

Codeine is a pro-drug of morphine. It is converted to morphine in the body and is 1/10th as potent as morphine (for example, 10 mg codeine is equivalent to 1 mg of morphine). But a proportion of patients have an in-born genetic inability to convert codeine to morphine and hence such people will not get pain relief with codeine. Other populations convert more readily and these patients can experience opiate toxicity. Codeine is more constipating than morphine. All opiates suppress cough so it is not necessary to use a codeine preparation to quiet a cough.

Tramadol is 1/5th to 1/10th as potent as Morphine. It may be useful in pain associated with a neuropathic component. Tramadol appears to be more emetogenic, but produces less constipation and dependence when compared with equianalgesic doses of morphine.

It is important to note that when access is not a problem, morphine in smaller equipotent doses may be used as a Step 2 drug.

**Steps for calculating the dose of oral Morphine**

1. Assess the severity of pain. Step 3 is considered if the pain is severe or when a trial of the step 2 drug does not relieve pain.
2. The usual starting dose for a patient with normal renal function is 5-10 mg 4 hourly. The patient is advised to take rescue doses for breakthrough pain between the regular doses.
3. The night dose is usually double that of other doses so as to avoid waking up in the middle
of the night. The sedation due to the extra dose is often helpful.

4. The first review should be within 2 days. The overall pain relief over that period is noted. If it is considered satisfactory, i.e. the pain scale stays < 3 most of the time and the patient becomes more functional, then total daily requirement for pain relief is calculated by adding the regular and the rescue doses. This total daily requirement is divided into 6 doses and continued.

e.g. Suppose a patient is on 15mg 4th hourly and he also takes two rescue doses each of 15 mg, then the total intake during a day is $(15 \times 6 = 90\text{mg}) + (15 \times 2 = 30 \text{mg}) = 90 + 30 = 120 \text{mg}$.

This is then divided by 6. Hence this person’s requirement may be calculated as 20mg 4th hourly. This is usually administered as 20 mg each on waking up, at 10 AM, 2 PM, 6 PM and 40 mg at bed-time. The person is still allowed to take a rescue dose of 20 mg if required.

5. The next review would be in the next 2 days to assess for stable pain relief with particular attention to bowel function and other adverse effects.

6. With 2 or 3 reviews over a week the average daily dose may be estimated and reviews can be less frequent.

7. Once the daily requirement of regular morphine for sustained pain relief is estimated, one may also consider converting the short acting formulation to equipotent slow release preparations based on the 24-hour requirement of morphine. For example, if morphine 20mg every 4 hours gives adequate pain relief around the clock, then the requirement in 24 hours is 120mg. Hence a 12 hour sustained release preparation of 60 mg can be prescribed twice daily.

8. The rescue dose for breakthrough pain should be given as immediate release morphine. It is generally calculated as equivalent to 1/6th of the patient’s current daily opioid dose. That is, a patient who is receiving 60 mg of sustained release morphine every 12 hours should have a rescue dose of $120 \text{mg}/6 = 20 \text{mg}$ of immediate release morphine Q4H.

The supply, stocking and dispensing of step 3 opioids are governed by the Narcotic Drugs and Psychotropic Substances Act – NDPS Act 1985 and by its recent amendment – the Narcotics Amendment Act, 2014.

Regulation of Step 3 Opioids

NDPS Act 1985 was primarily aimed at curbing misuse and diversion of opioids to illicit channels. It legislated such stiff penalties for even clerical errors that hospitals and pharmacies stopped stocking opioids. Between 1985 and 1998, consumption of step 3 opioids in India decreased about 70% of pre-1985 levels. In 1998, thanks to the initiative of palliative care activists, the government of India gave an instruction to all states to amend and simplify their narcotic rules. Unfortunately, only a few states complied.

At this time different states have different rules. Most of the time, multiple licenses from different governmental agencies are required. Due to these bureaucratic regulations, oral morphine is not available in most of India. It is estimated that only about 1% of the patients in need have access to morphine.

NDPS Amendment bill 2014

On February 21, 2014, the Parliament of India enacted the NDPS amendment bill which brings in uniformity of access to opioid analgesics throughout the country. Essentially the amendment shifts the responsibility for enacting state rules from the state Government to the central Government. Once the state rules are framed by the government of India and implemented, a single order by the drug controller of the state will be sufficient for any institution to stock and dispense morphine, subject to the applicant institution following minimum standards.
FENTANYL CITRATE

Fentanyl is a selective mu receptor agonist.
In India, it is available as injections of 50 ug/ml and as 72-hour transdermal patch formulation in strengths of 12.5, 25 and 50 μg/hour. There is a transmucosal preparation for oral/nasal administration that is available for quick relief of incident pain.

Considerations while using fentanyl patch

- Fentanyl is unsuitable for patients with unstable pain.
- Peak plasma concentrations are achieved after 12-24 hours and a depot reservoir remains in the skin for some 24 hours after the patch is removed.
- Rescue doses of opioid will be necessary during the first 24 hours of application.
- It is expensive.
- A reduction of laxative may be necessary when converting from morphine to fentanyl as the latter may cause less constipation.
- Patches have to be used on dry non-inflamed, non-irradiated, and hairless skin. It should stick well without wrinkles on the skin. The rate of absorption may change in the presence of fever, external heat or a hot water soak.
- Daily dose of 50-60 mg of oral morphine is equivalent to 25 mcg/hr transdermal fentanyl. In both cases immediate release morphine should be available to manage breakthrough pain.
- One in ten patients who have had their pain controlled by morphine may experience a withdrawal reaction when switched over to fentanyl. They may require oral morphine on a PRN basis to manage the withdrawal symptoms for a day or two.

Patient cannot have their pain medications titrated using patch delivery.
**Some specific indications for using transdermal fentanyl.**

a) Dysphagia.

b) Intolerable side effects with morphine - nausea, vomiting, constipation, disorientation, delirium.

c) Renal failure.

d) Dislike for tablets or poor compliance to oral therapy

**Ways of improving effectiveness of the WHO Analgesic Ladder**

1. Manage the known side effects of the medicines actively from the first prescription onwards e.g. prophylactic proton pump inhibitors in high risk patients on NSAIDs; stimulant laxative with opioids.

2. While prescribing, educate and provide information on where the medicines are available: Oral Morphine is available in hospitals and centres that are “Recognised Medical Institutions” (RMI) which have been authorised by the state drug controller in the states with simplified NDPS rules in our country.

3. Pharmaco-economics: Many patients may need long term medications for pain relief. Hence due attention is to be paid in choosing medications that would keep the cost of the treatment as low as possible.

4. Communicate with patients and understand phobias that exist regarding certain groups of drugs, especially opioids. Compliance will be better when questions are answered and doubts are addressed.

5. Review and re-evaluate for changes in clinical condition, side effects, responsiveness to treatment, or appearance of new pain.
# MANAGEMENT OF OPIOID SIDE EFFECTS

Table 3.9 – Common side effects of opioids

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Incidence</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>≥ 95%</td>
<td>Stimulant laxatives (e.g. bisacodyl 10 mg HS) Softeners/lubricant (liquid paraffin) Bulk-forming laxatives are unsuitable for opioid-induced constipation.</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>33 %</td>
<td>Usually self-limiting in a week. Treat with: haloperidol 1-3 mg HS or metoclopramide 10 mg tds. Prophylactic anti-emetics can be given for first 3 days of morphine therapy.</td>
</tr>
<tr>
<td>Sleepiness and tiredness</td>
<td>33 %</td>
<td>Often self-limiting in a week. Reduce dose and review if it persists.</td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td>Mouth care; soda bicarbonate mouth wash.</td>
</tr>
<tr>
<td>Urinary hesitancy due to prostate hyperplasia</td>
<td></td>
<td>Alpha blockers (tamsulosin 0.4 mg HS)</td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td>Keep skin moist. 5HT3 blockers: ondansetron 4-8 mg OD-BD Anti-histamines.</td>
</tr>
</tbody>
</table>

A number of different approaches may be used to manage persistent opioid-related side effects:

- Anticipate and treat the side effect with additional drugs. e.g. stimulant laxative for constipation.
- Use an alternative opioid with lesser side effect – fentanyl is less constipating than morphine possibly because of the nature of the molecule or the route of administration.
- Use an alternative analgesic or another route, such as spinal opioids, which may cause less systemic or central side effects.

The objective is to achieve effective pain management with improved sleep and function with minimal adverse effects.
SIGN SOF OVERDOSE WITH ORAL OPIOIDS

The symptoms of overdose are undue drowsiness, vomiting, confusion, myoclonus, delirium and hallucinations. Patients may have pin point pupils with morphine overdose. Respiratory depression is NOT common with oral morphine unless there is a deliberate or accidental overdose. If the medicine is titrated to achieve pain relief with regular review, an overdose can be avoided. Adequate hydration is important for managing states of overdose.

Table 3.10 – Signs of overdose with opioids and their management

<table>
<thead>
<tr>
<th>Signs of overdose</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>Dose reduction and anti-psychotics (haloperidol)</td>
</tr>
<tr>
<td>Myoclonic jerks</td>
<td>Dose reduction</td>
</tr>
<tr>
<td>Extreme drowsiness</td>
<td>Dose reduction</td>
</tr>
<tr>
<td>Respiratory Depression:</td>
<td>Titrated dose of IV Naloxone, skip next dose and reduce dose.</td>
</tr>
<tr>
<td>R.R &lt; 8-9 / minute; SaO2 &lt; 85%;</td>
<td></td>
</tr>
<tr>
<td>and pinpoint pupils</td>
<td></td>
</tr>
</tbody>
</table>

Opioid-induced respiratory depression:

The common misconception that oral morphine is associated with respiratory depression keeps medical professionals from prescribing this useful medicine. Pain antagonizes the central depressant effects of opioids and hence doses adequate for pain relief do not cause respiratory depression.

*Respiratory depression is NOT LIKELY, when opioid has been titrated according to the type and severity of pain with regular review.*

Opioid withdrawal symptoms and pain can happen if long-term opioids are abruptly stopped. Withdrawal syndrome is seen when the activity of the particular drug at the receptors is suddenly reduced due to reduction in dose, withholding the drug or using an antagonist. It is characterised by rhinorrhea, lacrimation, disorientation, hyperthermia, emesis, myoclonus, anxiety, agitation, delirium, abdominal cramps, yawning and diarrhea.

Naloxone is indicated only if significant respiratory depression is present. It is important to titrate the dose of naloxone carefully, to avoid acute opioid withdrawal. Naloxone has a half-life of 20 minutes. As the half-life of most opioids is longer than this, it is important to continue assessment of the patient and give naloxone at further intervals as necessary.
CLARIFICATION OF TERMS

Addiction

Addiction is characterised by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.

Physical Dependence

Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist.

Take home message in managing persistent pain

- Acknowledge pain
- Evaluate with attention to detail
- Provide explanation to the patient
- Aim for graded pain relief
- Respect patient’s expectations
- Review frequently
- The use of strong opioids is dictated by therapeutic need and response. Remember: not all pain responds to opioids.

Table 3.11 – Myths and facts about morphine.

<table>
<thead>
<tr>
<th>MYTHS</th>
<th>FACTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory depression is common with regular use of step 3 drugs.</td>
<td>Respiratory depression is very rare if the analgesic dose is appropriately titrated for pain relief.</td>
</tr>
<tr>
<td>All patients on step 3 drugs become addicted to them.</td>
<td>The chance of addiction with good monitoring is low.</td>
</tr>
<tr>
<td>Step 3 drugs are to be used for managing pain only in terminal illness.</td>
<td>Choosing the drug should be based on severity of pain and not on the stage of the disease.</td>
</tr>
<tr>
<td>Step 3 drugs are expensive drugs.</td>
<td>Morphine and methadone are among the least expensive medicines. Transdermal fentanyl is expensive.</td>
</tr>
<tr>
<td>The therapeutic range is narrow and toxic effects occur within the therapeutic range.</td>
<td>Oral formulations of step 3 drugs such as morphine have wide range of therapeutic efficacy and do not have ceiling effect. The dose may be gradually increased and individualized.</td>
</tr>
</tbody>
</table>
NOW LET US SEE HOW WE CAN MANAGE OUR PATIENT CHENNAYYA.

He has a mixed type of pain with both nociceptive and neuropathic pain. His pain is provoked by chewing. He also has a foul-smelling wound, which adds emotional, social and spiritual components to his pain.

For his background persistent pain of moderate severity, we could start him on:

- **Step 2 drug e.g. tramadol 50mg 6th hourly**
- **Non-opioid e.g. paracetamol 650 mg QID after food**
- **Local care for the foul smelling wound with metronidazole gargle (injectable metronidazole in saline) with additional powdered tablet metronidazole in biolinguae over the wound**
- **Antibiotic e.g. amoxicillin 500mg 8th hourly**
- **Amitriptyline 12.5 mg at bedtime, with a gradual increase in dose up to 50 – 75 mg at night for the neuropathic component**
- **If there is severe inflammation contributing to pain, ibuprofen 400 mg TID can be given after food, along with gastro-protectant such as omeprazole 20 mg OD on empty stomach. Ensure adequate hydration. Avoid if the patient is on steroids.**

The opioid may be increased later to morphine (instead of tramadol) in case of unsatisfactory pain relief or progressive disease. Education on mouth care and wound care are important contributors to relief.

Once the smell disappears, his social isolation will also improve. Building a therapeutic relationship through regular communication to understand his distress is important. The family could be involved in his care with appropriate communication by the multi-disciplinary team.
Test your knowledge

1. Tolerance develops to all the following adverse effects of oral morphine EXCEPT:
   a. constipation
   b. nausea and vomiting
   c. tiredness
   d. sedation

2. The most unsuitable group of laxatives to relieve morphine-induced constipation is
   a. stimulant
   b. bulk-forming
   c. osmotic
   d. stool softener

3. Which of the following is a toxic effect of oral morphine overdose?
   a. Urinary hesitancy/retention
   b. Respiratory depression
   c. Mild drowsiness
   d. Nausea/vomiting

Answer Key: 1. a; 2.b; 3.b

Suggested Reading
1. Introduction to Palliative Care by Robert Twycross, 4th Edition
Guidelines by the American Society of Interventional Pain Physicians (ASIPP) for responsible opioid-prescribing in chronic non-cancer pain21
(level of evidence is given in brackets)

1. Essential to establish medical necessity prior to initiation or maintenance of opioid therapy (EVIDENCE: good)

2. Comprehensive assessment and documentation is recommended before initiating opioid therapy, including documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. (EVIDENCE: good)

3. Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. (EVIDENCE: good)

4. Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. (EVIDENCE: good)

5. Urine drug testing (UDT) and prescription monitoring programs are recommended for implementation from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. (EVIDENCE: good) This may be difficult in Indian clinical settings.

6. A consultation with a pain specialist may be helpful when initiating high-dose opioid therapy (EVIDENCE: fair)

7. Ordering diagnostic tests such as x-rays and laboratory tests must be done thoughtfully, as tests can heighten fear, restrict activity, and cause requests for increased opioids or cause maladaptive behaviours. (EVIDENCE: good)

8. The relative and absolute contraindications to opioid use in chronic non-cancer pain must be evaluated including respiratory instability, acute psychiatric instability, uncontrolled suicide risk, active or history of alcohol or substance abuse, allergy to opioid agents, co-administration of drugs capable of inducing life-limiting drug interaction, concomitant use of benzodiazepines, active diversion of controlled substances, and concomitant use of heavy doses of central nervous system depressants. (EVIDENCE: fair to limited)

9. Constipation must be closely monitored and a bowel regimen when opiates are prescribed. (EVIDENCE: good)

10. Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities if there is significant improvement in physical and functional status and minimal adverse effects.

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INTERVENTIONAL TECHNIQUES FOR MANAGEMENT OF PAIN

Objectives
1. Enumerate common intervention techniques available for managing persistent pain.
2. Describe the fundamental criteria for choosing intervention techniques for a pain patient.
3. Recognize when to refer a patient for interventional pain procedures.

Definition
Interventional pain management is the discipline of medicine devoted to the diagnosis and treatment of pain and related disorders by the application of interventional techniques in managing pain, independently or in conjunction with other modalities. Interventions include trigger point injections, nerve blocks, autonomic or sympathetic plexus blocks, minimally invasive spinal interventional techniques (ablation of targeted nerves, intrathecal infusion pumps or spinal cord stimulators).

Interventional techniques are possible options for patients with failed oral or transdermal analgesic therapy. This section familiarises the student with few of the commonly applied techniques.

Spinal interventional techniques
These techniques have traditionally evolved for managing persistent back pain. The low back pain may occur because of the involvement of the intervertebral discs, facet joints, sacroiliac joints, ligaments, fascia, muscles and nerve roots. Diagnostic blocks can confirm that these structures are the causative sites for the pain syndrome. The common interventions are:

1. Epidural injections – Thoracic, lumbar or cervical. The approach may be inter-laminar, trans-foraminal or caudal based on the source of pain.
2. Facet joint blocks – intra-articular injections, medial branch blocks, or neurolysis of medial branches e.g. radio-frequency ablation
3. Sacroiliac joint injections – for lower back pain with identified source
4. Spinal cord stimulation – this has been utilised for neuropathic pain of failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS). It is an intervention of last resort.

The common drugs used neuraxially in low back pain
- Methylprednisolone 40-80mg
- Triamcinalone acetonide 40-80 mg
- Betamethasone sodium phosphate (or non-particulate formulation ) 6-12 mg
- Dexamethasone sodium phosphate 8-16 mg
Interventional techniques in cancer

Interventional technique may be considered as a strategy at any phase of the management of severe pain or as the 4th step of analgesic ladder. A regional block might bring relief by blocking the transmission of nociception from the diseased area. A peripheral nerve block using local anaesthetic is useful for quick relief of severe nociceptive pain. For example, pain due to an osteogenic sarcoma of the femur in a child may be temporarily controlled with a triple block in the inguinal region (if this area is not invaded by the tumour) as a short term measure, while waiting for analgesics to take effect. However, to maintain pain relief on long term, oral pharmacotherapy is ideal as it is affordable and sustainable in the domiciliary setting.

Neuraxial analgesic infusions

In the case of pain which is not controlled by oral medications, continuous infusions of opioid/local anesthetic combinations may be considered, with catheters placed neuraxially i.e. in the epidural or spinal spaces. The cost of the technique, materials and maintenance required could be cost prohibitive. It is a highly individualised decision to be taken with due consideration of the benefit, the duration of utility and the adverse consequences.

Neuraxial analgesic measures may be considered for patients with continuous excruciating pain involving major nerve plexus e.g. brachial/lumbo-sacral plexopathy due to spread of tumour. For this, the patients are to be referred to specialized doctors in the field of interventional pain management.

The common drugs that are used as infusions neuraxially

- Opioids: morphine (0.03-0.05mg/ml @2-5ml/hr), fentanyl (1-2ug/kg/hr). The concentration and the volume used per hour changes when the infusion is used intrathecally.
- Local anaesthetic agents: bupivacaine (0.0625% - 0.125% @ 5 ml/hr), ropivacaine (0.1% @ 5 ml/hr)

Neurolysis

Neurolytic techniques in general have a narrow risk-benefit ratio and have been largely replaced by neuraxial analgesic techniques as mentioned above. However, the indications for interventional techniques are less frequent in pain due to cancer, as the pain is not limited to the distributions of a nerve or a plexus nor are they purely somatic or autonomic in nature. Usually cancer pain has mixed etiologies with pathological neuroplasticities and additional major psycho-social components.

**Possible Indications for Neurolysis**

1. In patients with severe, intractable pain in whom less aggressive manoeuvres are ineffective or intolerable because of either poor physical condition or the development of side effects.

2. The goal of neurolysis i.e. analgesia, may produce undesirable side effects, including sphincter weakness and limb paralysis. In most but not all cases, these are unacceptable complications. Hence the prognosis and quality of life are significant considerations.

3. The risk of de-afferentation pain is significantly increased after a neurolytic block to a peripheral nerve.

4. Patients / family are made cognizant of pros and cons of making or not making the choice as well as the alternatives for handling the situation.

**Neurolytic blocks may be:**

- Chemical – 50-100% alcohol or 7-12% phenol
- Thermal – cryotherapy, radiofrequency thermo-coagulation.

**Preconditions for successful block**

1. Pain that has not responded to pharmaceutical interventions, or other non-surgical management, including physical therapy.

2. Duration of pain of at least 3 months intermittently or continuously with average pain levels of ≥ 6 and causing significant functional disability.

3. Availability of trained specialist pain physician.

4. Clarity on mechanism of the particular pain state, so that the choice of technique is informed and appropriate.

5. No contraindications related to the nature of the procedure, needle placement, or sedation.

6. No history of allergy to contrast administration, local anaesthetics, steroids, or other drugs.

7. Fully informed consent.

8. Diagnostic block using local anaesthetic is mandatory to validate indication for a future neurolytic block. If the painful area shows definite response to diagnostic block with a local anesthetic, then one may proceed with neurolysis of the same.
A few situations where neurolytic blocks are commonly employed:

- In areas where pain is limited to a circumscribed section, such as rib invasion/metastases, the pain may be treated with intercostal neurolysis.
- Stellate ganglion block is useful to evaluate or treat the autonomic component in upper limb or facial pain.
- Gasserian ganglion block at the level of foramen ovale at the base of the skull, or its branches, using radiofrequency technique or neurolytic solutions may benefit certain kinds of facial pain.
- Coeliac plexus block for pain limited within the viscera supplied by it.
- Lumbar sympathetic plexus may be blocked for managing ischemic pain as seen in patients with thrombo-angitis obliterans.
- Superior hypogastric plexus block may help for pain of sympathetic origin from cervical cancer or for any type of pelvic pain except ovarian pain.

Neurolysis rarely is permanent, and pain returns after an interval, either from a re-growth of neural structures or by progression of the underlying disease beyond the treated area.

Surgical interventional techniques

Surgical neurolysis is generally being replaced by interventions by pain medicine specialists. Certain situations merit limited surgical considerations, such as the use of percutaneous vertebroplasty with injection of methyl-methacrylate to stabilize vertebra weakened by lytic disease. Percutaneous chordotomies and rhizotomies are among other procedures undertaken. The risk–benefit ratio is very variable and the decision for considering surgical interventions are highly individualised.

Conclusion

Pain is a multi-factorial condition. Much of the needless suffering may be mitigated by adequate communication with the patient in understanding the nature of pain, building rapport and confidence and competent application of current knowledge in pain medicine. Being available throughout the trajectory of chronic diseases with regular review and evaluation through a multi-disciplinary team approach is a necessity for positive outcomes and improved quality of care. The role of non-pharmacological interventions such as physical therapy and occupational therapy is to be utilised early. The WHO analgesic ladder drugs are useful in 75% of cancer patients up to terminal stages. They are to be used with awareness of their pharmacology and altered physiology of patients with advanced illness. The use of interventional techniques for pain is an option, yet an extremely challenging decision and requires clarity regarding etiology, patient’s condition and expected outcomes.

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