Indian Society for Study of Pain, Cancer Pain Special Interest Group Guidelines on Pharmacological Management of Cancer Pain (Part III)

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Abstract

The Indian Society for Study of Pain (ISSP), Cancer Pain Special Interest Group, guidelines on pharmacological management of cancer pain in adults provide a structured, step-wise approach which will help to improve the management of cancer pain and to provide patients with a minimally acceptable quality of life. The guidelines have been developed based on the available literature and evidence, to suit the needs, patient population, and situations in India. A questionnaire based on the key elements of each sub draft addressing certain inconclusive areas where evidence was lacking, was made available on the ISSP website and circulated by E-mail to all the ISSP and Indian Association of Palliative Care members. Antidepressants and/or anticonvulsants should be used to treat neuropathic cancer pain and the dose should be titrated according to the clinical response and side effects. External beam radiotherapy should be offered to all patients with painful metastatic bone pain. There is evidence on the use of ketamine in cancer neuropathic pain, but with no beneficial effect, thus it is not recommended.

Keywords: Bone pain, breakthrough pain, cancer pain management guidelines, cancer pain management, Cancer Pain Special Interest Group, Indian Association of Palliative Care, Indian Society for Study of Pain, opioids, WHO analgesic ladder

Introduction

Although pain is often the primary presenting symptom of cancer and despite the presence of guidelines and the availability of opioids, cancer pain still remains undertreated. Although there are many guidelines available in the literature, they take into account the scope of practice only in the respective countries. Since the patient population is different with respect to the Indian context, they may not work well. Conditions of medical practice are not only different in our country but are also variable, depending on the type of institution/center that one works in. These guidelines are developed to improve the management of cancer pain and to provide the patients with a minimal acceptable quality of life.

Methods

Literature search [Appendix IV] was carried out using PubMed, MEDLINE, COCHRANE DATABASE, GOOGLE SCHOLAR, and OVID Search engine. The search included studies published in English language until November 2018. Where evidence is lacking, recommendations were made by consensus (good clinical practice), following extensive discussion among the committee members and considering the

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results of the questionnaire [Appendix V] circulated during the meeting, and also were made available on the Indian Society for Study of Pain (ISSP) website and circulated by E-mail to all the ISSP and Indian Association of Palliative Care (IAPC) members.

Opioids in renal and liver impairment

Renal impairment (RI) is a common problem encountered in patients with advanced cancer due to age, concomitant illnesses, chemotherapy, or the cancer itself. The metabolites of the opioids are altered as well as accumulated in the presence of RI.[1,2]

Morphine

Morphine is metabolized in the liver to two main metabolites, morphine-3-glucuronide (M3G) (55%) and morphine-6-glucuronide (M6G) (10%), which are excreted renally along with 10% of the parent drug.[3] M6G is a potent analgesic and central nervous system (CNS) depressant. M3G decreases seizure threshold. In patients with renal and/or liver impairment, morphine should be used in lower doses and at longer dosing intervals while SR preparations should be avoided.[4,5]

Fentanyl

Fentanyl is metabolized in the liver primarily to norfentanyl and other inactive and nontoxic metabolites.[3] In liver disease, the metabolism of fentanyl is affected mainly by decreased hepatic blood flow rather than severe hepatic dysfunction and is therefore relatively safe to be used.[4,5]

Tramadol

Tramadol is metabolized in the liver to the active metabolite, O-desmethyltramadol (M1) which contributes to its analgesic effect. Both parent drug and metabolite undergo renal excretion, with approximately 90% of the oral dose excreted by the kidneys, therefore it can accumulate in renal insufficiency.[6] Significant respiratory depression has been reported in patients with severe renal insufficiency, which could be explained by the accumulation of the metabolite M1, which has a high affinity for opioid receptors.[7]

Methadone

Methadone is primarily excreted in the feces, with approximately 20% excreted unchanged in urine. Methadone tends to accumulate in tissues with chronic use, has a long and variable half-life, and is highly protein bound.[8] There is no clinical evidence for the accumulation of methadone or its metabolites, therefore suggesting that methadone is safe to use in patients with renal disease.[9] It is advised to monitor these patients for signs of opioid toxicity.

Codeine

Renal clearance of codeine and its metabolite codeine-6-glucuronide is reduced in patients with RI.[10] In addition, codeine is metabolized to morphine and its metabolites that also accumulates in patients with RI.[5] Codeine should be avoided in patients with severe RI.[4]

Table 1: Antidepressants with number needed to treat and number needed to treat to harm

Antidepressant group[1]	Name	NNT (combined)	NNH (combined)
Tricyclic antidepressants	Amitriptyline Imipramine Desipramine Nortriptyline	3.6 (amitriptyline mainly studied)	13.4 (amitriptyline mainly studied)
SNRI	Duloxetine Venlafaxine	6.4 (combined)	11.8 (combined)

Caution (applies to all): Ischaemic heart disease, conduction defects, closed angle glaucoma, prostatic enlargement. Adverse effects (applies to all): Sedation, dryness of mouth, urinary retention, constipation. Venlafaxine can cause ventricular arrhythmias in established heart disease. SNRI: Serotonin and noradrenaline reuptake inhibitor, NNT: Number needed to treat, NNH: Number needed to treat to harm

Buprenorphine

Buprenorphine is metabolized mainly to norbuprenorphine, which is the only metabolite thought to have analgesic activity with forty times potency less than the original compound.[11] Unchanged buprenorphine is mainly excreted in the feces and its metabolites are mainly excreted in the urine.[11] Buprenorphine is generally safe to use in RI.[12]

Adjuvant medications

Adjuvant analgesics are drugs that are not primarily analgesics, but in specific conditions can exhibit analgesic properties. Adjuvant analgesics are prescribed mainly in mixed cancer pain such as neuropathic cancer pain,[13] chemotherapy-induced peripheral neuropathy, and metastatic bone pain (mBP). They are prescribed along with an opioid or by themselves.

Adjuvant analgesics for neuropathic pain

Antidepressants

Antidepressant drugs have been prescribed as an adjuvant for the management of neuropathic pain along with an opioid[13] [Table 1]. Constant vigil should be maintained for serotonin syndrome when used in conjunction with serotinergic medications. They are started at lower doses and increments in dosage are done once in 5–7 days.

Anticonvulsants

Pregabalin and gabapentin are the commonly prescribed adjuvants and act by modulating the function of α2-δ subunit of voltage-gated calcium channels in the dorsal horn of the spinal cord, thus decreasing the release of substance *P* and glutamate. Pregabalin exhibits an additional anxiolytic activity.

A prospective, randomized, double-blind, placebo-controlled study examined pregabalin versus common neuropathic pain analgesics (gabapentin and amitriptyline) and placebo and concluded that pain scores were statistically significantly lower in the amitriptyline group ($P = 0.003$) and gabapentin group ($P = 0.024$). The percentages of patients requiring morphine at the last visit were 56.7% (amitriptyline), 33.3% (gabapentin), 16.7% (pregabalin), and 100% (placebo).[14]

Table 2: Bone specific agents and different malignancies

Malignancy	Bisphosphonates studied	RANKL-antagonist	Best bisphosphonate
Breast cancer	Pamidronate, ibandronate and zolendronate[12,13]	Denosumab[14]	Zolendronate
Prostate cancer[15]	Zolendronate	Denosumab	Zolendronate
Other solid tumors metastatic to bone[16]	Zolendronate, etidronate, pamidronate, clodronate	Denosumab	As per the primary malignancy
Multiple myeloma[17]	Zolendronate, pamidronate, clodronate	Denosumab	Zolendronate and pamidronate equal efficacy. Zolendronate superior to clodronate

Number needed to treat (NNT) for pregabalin[13] is 7.7, while number needed to treat to harm (NNH) is 13.9.

NNT for gabapentin[13] is 6.3, whereas NNT for gabapentin extended release is 8.3, whereas, NNH is 25.6 and 31.9, respectively.

Bone pain

Metastatic bone disease is most commonly seen with specific cancer types, notably those arising from the breast, prostate, lung, and kidney, as well as multiple myeloma.[15] Pain is a debilitating symptom, with skeletal-related events (SRE) leading to loss of mobility and increased dependency that affect their health-related quality of life.[16] Bisphosphonates and RANKL antagonists are bone-specific agents [Table 2][17-22] aimed at relieving bone pain and hypercalcemia and reducing the incidence of SRE.[23] External beam radiotherapy (RT) and radioisotopes also play an important role in the management of mBP.

A single dose of 8 Gy RT gives a profound pain relief in the majority of uncomplicated mBP.[24] RT is the first-line treatment for the majority of patients with metastatic spinal cord compression (mSCC). The ideal dose schedules of 20 Gy in 5 fractions or 8 Gy in two fractions or one fraction are very effective.[25,26] A single dose of 8 Gy can also be considered for re-irradiation, if there is a recurrence of mBP.[27] In mSCC, steroids should be started immediately, after the diagnosis, with dexamethasone being the commonly used drug. Evidence on loading dose of steroids is limited, but usually doses ranging from moderate (8 mg/day) to ultra-high levels (36–96 mg/day preceded by a bolus of 10–100 mg intravenous) have been advocated in literature and need to be tapered gradually over 2 weeks.[28] Surgery should be advised in patients with spinal instability and recurrence of pain after RT.[29]

Bisphosphonates are the synthetic analogs of pyrophosphates found in the bone matrix, and when administered concentrate primarily at the active remodeling sites. They act by inducing osteoclast apoptosis. RANK ligand antagonist prevents the activation and survival of osteoclasts. When no inflammatory cytokines are released, inflammatory process is dampened, with less stimulation of the highly innervated periosteum, thus reducing pain.[30,31]

A Cochrane meta-analysis reviewed thirty randomized controlled studies to determine the effectiveness of bisphosphonates for the relief of pain from bone metastases.

NNTwasfoundtobe11at4 weeksand7at12 weeks. NNH in terms of adverse effects was 16 at 12 weeks, warranting discontinuation of therapy. Patients who received bisphosphonates had reduced usage of analgesics compared to placebo.[32]

In a systematic review evaluating the analgesic effect of zolendronate and denosumab on bone pain, the quality of evidence of the 43 articles that met the inclusion criteria was very low. Twenty-two (79%) of the 28 placebo-controlled trials found benefit in analgesic property for bisphosphonates. Pain relief was not assessed in the studies on denosumab. Evidence to support the analgesic role of bisphosphonates and denosumab is weak. Bisphosphonates and denosumab are beneficial in preventing pain by delaying the onset of bone pain rather than providing analgesic benefits (denosumab 9.7 vs. 5.8 months for bisphosphonates, $P = 0.0024$). There was no difference between the two arms, in the time needed to obtain a noticeable decrease in pain intensity once present.[33]

A randomized double-blind study evaluating 1904 men with castration-resistant prostate cancer and bone metastases found denosumab to be better than zoledronic acid for the prevention of SREs. The time to first SRE was 20.7 months with denosumab versus 17.1 months with zoledronic acid ($P = 0.0002$, hazard ratio 0.82, confidence interval [CI] = 0.71–0.95).[34]

Both bisphosphonates and denosumab are generally well tolerated. Zolendronate is associated with episodes of acute-phase response such as transient increase in bone pain, fever, and myalgia, which peak in 24–48 h and resolve within 72 h. Renal dysfunction associated with zolendronate requires regular evaluation of creatinine/creatinine clearance.[35]

Osteonecrosis of the jaw is a complication seen with both therapies. They are associated with a history of tooth extraction, poor oral hygiene, and use of dental appliances.[35] Hypocalcemia is seen more with denosumab. Regular monitoring of calcium levels is needed. Vitamin D and calcium supplementation is strongly advised.[36] In selected group of patients who present with multiple osteoblastic lesions, radioisotopes such as strontium, rhenium, and radium-223 had been extensively studied.[37,38] A Cochrane meta-analysis reviewed 15 studies to determine the efficacy and safety of radioisotopes in patients with bone metastases and observed a small benefit of radioisotopes for complete relief (risk ratio [RR]: 2.10, 95% CI: 1.32–3.35; NNT to benefit = 5) and complete/partial relief (RR: 1.72, 95% CI: 1.13–2.63; NNT = 4) in the short-and medium term and concluded that radioisotopes provide complete reduction in pain over a period of 1 to 6 months, but severe adverse effects

such as leukocytopenia and thrombocytopenia are frequently associated.[37] Except for radium-223, the rest had shown minimal beneficial effects. Radium-223 has been shown to improve SREs and also prolong survival.[38]

Corticosteroids

Corticosteroids are used as adjuvant analgesics for their anti-inflammatory properties as well as the postulation that this group of medication exerts effect on all the four stages of pain and nociception. Their anti-inflammatory effect is exerted due to the inhibition of inflammatory cytokines and prostaglandin production. The resultant decrease in inflammation leads to decrease in capillary permeability reducing the edema.[39]

Corticosteroids are used in clinical situations of inflammation and edema – in confined spaces including intracranial, spinal, pelvic, or retroperitoneal spaces. They are also used in the relief of pain from space-occupying lesions of brain, spinal cord, nerves, liver, and soft tissues.[40] Dexamethasone is the most studied corticosteroid as it has the least mineralocorticoid activity and due to its long duration of action, can be used once a day.

A randomized, placebo-controlled, double-blind trial, evaluating pain management in adult patients with advanced cancer, concluded that there was no statistically significant relief of pain or reduction in opioid consumption with methylprednisolone versus placebo (P = 0.88 and P = 0.95, respectively). The corticosteroid therapy improved fatigue (P = 0.003), appetite (P = 0.003), and patient well-being (P = 0.001).[41]

Corticosteroids do not improve opioid analgesia or reduce opioid consumption in advanced cancer patients.[42]

A systematic review on the role of corticosteroids in providing analgesia found that moderate doses of corticosteroids equivalent to methylprednisolone 32 mg or dexamethasone 8 mg daily are well tolerated for up to 7 days.[43]

Corticosteroids could make an individual susceptible to adverse effects such as predisposing to infection, hyperglycemia, insulin resistance, proximal myopathy and catabolic effects, skin changes, and adrenal insufficiency. Advanced cancer patients are particularly vulnerable. While prescribing, the risk–benefit balance should be considered.[44]

Ketamine

N-methyl-d-aspartate (NMDA) receptors are present in the periphery as well as the CNS and are activated when stimulated by the glutamate and aspartate released in response to activated peripheral pain fibers. Acute and chronic stimulation lead to the "wind-up phenomenon" of peripheral pain fibers (A-delta and C) producing symptoms of both allodynia and hyperalgesia, especially in patients with neuropathic pain.[45]

Ketamine is a dissociative anaesthetic. The mechanism of action is non-competitive blockade of the NMDA receptor. The indication for the use of ketamine as an adjuvant in cancer pain management is when pain is unresponsive to opioids or when opioid tolerance occurs.[46] The use of ketamine is restricted due to its adverse effects which include psychomotor retardation and hallucinations.

A recent review of literature from the Cochrane database and from an independent review article, reports the absence of sufficient evidence of benefit of ketamine as an adjuvant in cancer pain.[47,48] In a randomized controlled trial, analgesic effect was evaluated between ketamine and placebo among cancer patients who had chronic, chemotherapy-induced neuropathic pain. Of the 204 patients randomized, 74.7% were in remission and 97.6% were on medications for neuropathic pain. None were receiving morphine. There was no statistical difference between the two arms for analgesic benefit (P = 0.75).[49] A randomized, double-blind, placebo-controlled study conducted to assess the efficacy of ketamine in patients suffering from cancer pain refractory to opiates did not find benefit of morphine–ketamine combination in refractory pain.[50]

Anticholinergics and somatostatin analog

Malignant bowel obstruction can lead to colicky abdominal pain that can be very debilitating. Anticholinergic drugs reduce the propulsive gut motility and decrease intraluminal secretions, thus reducing the colicky pain.

Octreotide is a somatostatin analog that inhibits the secretion of gastric, pancreatic, and intestinal secretions and reduces gastrointestinal motility.

Table 3: Summary of recommendations

Recommendations	Level of evidence
Opioids should be used with caution in patients with renal and hepatic impairment (Grade C)	IV
Codeine should be avoided in patients with renal impairment (Grade C)	IV
Antidepressants and/or anticonvulsants should be used to treat neuropathic cancer pain and the dose should be titrated according to the clinical response and side effects (Grade A)	Ib
External beam radiotherapy should be offered to all patients with painful metastatic bone pain (Grade A)	Ia
Steroids should be started in patients with metastatic spinal cord compression (Grade B)	IIa
Bisphosphonates to be considered as part of the therapeutic regimen for the treatment of patients with metastatic bone pain (Grade B)	IIa
Denosumab should be considered as a valid alternative to bisphosphonates for the treatment of patients with/without pain due to metastatic bone disease from solid tumours (Grade A)	Ia
Radioisotopes should be considered for short to medium term pain relief keeping in mind the serious adverse effects (Grade A)	Ia
Steroids should be started in patients with metastatic spinal cord compression (Grade B)	IIa
There is an evidence on use of ketamine in cancer neuropathic pain, but with no beneficial effect, thus not recommended (Grade A)	Ia
Use of anticholinergics and somatostatin analogue is recommended for use in inoperable malignant bowel obstruction in pain (Grade A)	Ia

Researchers in a prospective, randomized clinical trial[51] concluded that all the patients with inoperable malignant bowel obstruction should undergo antisecretory drug treatment and that octreotide should be considered as the first-choice antisecretory drug. Another study concluded that a combination of octreotide with an anticholinergic[52] can be very effective in the symptom management of inoperable bowel obstruction in terminal cancer patients.

Conclusion

The Indian Society for Study of Pain (ISSP) cancer pain SIG guidelines on pharmacological management of cancer pain in adults emphasizes the importance of adjuvant analgesic medications in the form of antidepressants and or anticonvulsants to treat cancer neuropathic pain [Table 3]. Radiotherapy plays an important role in the treatment of bone metastases. Denosumab and bisphosphonates too play an important role in skeletal metastatic pain.

We believe that the ISSP cancer pain SIG guidelines on pharmacological management of cancer pain in adults will help pain specialist, anaesthesiologists, palliative care specialists and others who are involved in cancer pain care, in the safe management of cancer pain and to provide the patients with a minimally acceptable quality of life.

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Disclaimer

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. These guidelines should neither be construed or serve as a standard of care.

These guidelines do not represent the minimum standard of practice, nor are they a substitution for good clinical judgment. These guidelines need to be used in conjunction with patient assessment and may be individualized as per patient need.

These guidelines were developed in 2018-2019 and may be reviewed again in 2024 or sooner, based on the availability of new evidences.

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Conflicts of interest

There are no conflicts of interest.

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Appendix IV: Literature search

The following terms or MESH terms were used either in combination or single:

"Pain"[Mesh], "Prevalence"[Mesh], "Signs and symptoms"[Mesh], "Syndrome"[Mesh], "Diagnosis"[Mesh], presentation, "Neoplasms"[Mesh], tumours, cancers, physical assessment", "Pain Measurement"[Mesh], "pain scale'', psychosocial, assessment, "cognitively impaired', "psychological distress", distress, "Emotions"[Mesh] "Nursing"[Mesh], "prime assessor", "Palliative Care"[Mesh], "supportive care'', "cancer pain management", "Patient-Centered Care"[Mesh], "Patient Care Team"[Mesh], "Patient Care Management"[Mesh], "Primary Health Care"[Mesh], "Physicians, Family"[Mesh]), interdisciplinary, Education"[Mesh], outcome, barrier, "World Health Organization"[Mesh], "Guideline "[Publication Type], "cancer pain ladder", "World Health Organization three step analgesic ladder"[Mesh], Drug Therapy"[Mesh], "Analgesics, Opioid"[Mesh], "administration and dosage"[Subheading], titration, "breakthrough pain", "Drug Tolerance"[Mesh], "Adjuvants, Pharmaceutic"[Mesh], "adjuvant analgesics", "pregabalin "[Substance Name], "Ketamine"[Mesh], "Dexamethasone"[Mesh], corticosteroid, "opioid rotation", "opioid switching", "alternative opioid", "Bisphosphonates"[Mesh], "Sedation score", "Morphine protocol", "Radiotherapy"[Mesh], "Soft Tissue Neoplasms"[Mesh], "Behaviour Therapy"[Mesh], "Cognitive Therapy"[Mesh], "Physical Therapy Modalities"[Mesh], "Acupuncture"[Mesh], "Massage"[Mesh], "Exercise"[Mesh], "Exercise"[Mesh], "Nerve Block"[Mesh], "Injections, Spinal"[Mesh], "intrathecal therapy", "Vertebroplasty"[Mesh], "follow-up", "Physician's Role "[Mesh], "community care", "home program*", "general practitioner", hospice, "pain clinic", "Outpatients"[Mesh], "Outpatient Clinics, Hospital"[Mesh], "Ambulatory Care"[Mesh]

Appendix V: Cancer pain management questionnaire

1. How many patients of cancer pain do you manage per month?
2. What is the most frequent cancer pain that you encounter in your daily practice?
3. What are the clinical presentations of cancer related pain?
4. What are the methods used for clinical assessment of cancer pain?
5. What are the principles of management of pain in patients with cancer?
6. What is the WHO Analgesic Ladder? What are its principles? How effective is it in clinical practice?
7. Do you follow WHO step ladder approach for cancer pain management?
8. What do you prefer for step II and step III of WHO ladder?
9. What non-pharmacological techniques do you use to manage Cancer Pain
10. Do you screen all patients of substance abuse? If yes, which scale do you use.
11. What medications do you use to manage cancer pain
12. What are the major side-effects you observe due to pharmacological management and how do you manage it?
13. What are the adjuvant analgesics in cancer pain management?
14. What are the pharmacological strategies for breakthrough pain and other acute pain crises?
15. What are the roles of anti-cancer therapy in the management of cancer pain?
16. Do you manage patients using Interventional Techniques? If yes, which interventional techniques and in what percentage of patients?
17. What are the relative efficacy and safety of current invasive treatments for the treatment of cancer-related pain?
18. Do you think current treatment guidelines for cancer pain management are sufficient? If no, what changes do you suggest?
19. According to you, what steps need to be taken to spread the awareness regarding cancer pain management?