Review Article

The Unheard Pain of Cancer Patients

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ABSTRACT

Cancer pain is multidimensional and complex mechanism rarely presenting as a pure neuropathic, visceral, or somatic pain syndrome. Rather, it may involve inflammatory, neuropathic, ischemic, breakthrough pain mechanisms at multiple sites. Despite recommendation and demonstration of patients' need, these needs are not being met. Since two decades, a trend has been set to exclude pain specialist from mainstream cancer pain management, they are being called during the end stage making them the 'last resort'. Thus patients are missing out on benefits of multidisciplinary care combining palliative care and pain medicine. Morphine licensing is still a very painful procedure for the institutions trying to provide pain relief to the cancer patients and due to this troublesome procedure of morphine licensing many patients do not get adequate analgesia and die in pain. This review article highlights the importance of recognizing cancer-related pain and the need to optimize management. It emphasizes on pain management for the cancer population with evidence-based multimodal and mechanism-based treatments and finally to strengthen the relationship between palliative care, oncology, and pain medicine.

Introduction

It is people and families who experience pain and not just the nerve endings.[1] A patient of prostatic carcinoma (CA) with extensive bony metastasis and intense unrelieved pain for weeks expresses his desire to commit suicide. A lady with cervical CA wants active euthanasia but when the pain was relieved, her interest in life was rekindled and she wanted to spend the remaining time with her children and husband. Such are the grave consequences of pain in CA patients. Before the actual death, the patient dies so many times. It has been reported that more than 80-90% CA patients develop pain before death.[2] Whenever a patient is diagnosed of CA; pain is one dreaded consequence feared both by the patient and families. Although advances have been made in the management of pain, patients still suffer from uncontrolled pain associated with anxiety, depression, suicidal tendency, and many fear pain more than death.[3,4] Pain management therefore becomes an utmost responsibility of all the physicians and a basic human right, which every patient deserves. Lot of physician and patient-related barriers prevent the delivery of appropriate analgesia. Stringent narcotic rules in many countries make it difficult for the patients' to access opioid medicines. The proper management of CA pain requires a correct diagnosis of the type of pain, right choice of analgesics, and adjuvant analgesics, management of break through pain, correct use of conversion ratios when shifting in between analgesics, correction of the correctable causes, uninterrupted supply of opioid analgesics, management of resistant CA pain and use of nonpharmacological management for control of pain. Table 1 shows the classification of pain, mechanism of action, symptoms and its pharmacological management.

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The four dimensions of pain

Many times we insensitively communicate to the patient that "nothing more is left and that this is all that I could do", failing to realize that by saying so we are not only conveying a "do not disturb me anymore" attitude but also snatching away whatever little hope is left with him for survival. The persistent pain of CA patients not only means the physical pain, but also encompasses the psychosocial, social, and spiritual aspects of suffering. Sometimes pain may be used as a way of expression by the patient as "I am incurable and I am dying" therefore, physicians when treating such difficult to

comprehend pain must have a very broad outlook toward pain as total pain where the physical (pain, insomnia, fatigue), psychosocial (feeling of helplessness, anger at diagnosis, fear of death), social (loss of job, position, feeling of abandonment), and spiritual (purpose of life, why me ?) components of pain are addressed very meticulously.[5] One must also evaluate the type of physical pain, in terms of quality, radiation, and severity of pain and classify pain in terms of nociceptive, neuropathic, and sympathetically mediated pain. Pain may be graded for severity using a scale of 0-10 for adults or for children by using Wong Baker's scale. Figure 1 depicts the Wong Baker's scale for assessment of pain in children. The cause of pain in CA patients may be due to noncarcinogenic origin like osteoarthritis, postherpetic neuralgia, muscle spasms, or postchemotherapy peripheral neuropathy and hence must be evaluated for the cause to treat the correctable. In 15% of the advanced CA patients, none of their pain is caused by CA itself.[5]

Classification of CA pain

Chronic pain related to cancer can be considered as tumor-induced pain (85%), chemotherapy-induced pain (vincristine and vinblastine), and radiation therapy-induced pain (postradiation pain, plexopathy, myelopathy) or general debility associated pain.[5,7,8] The task force on Cancer Pain of International Association for the study of Pain (IASP) conducted an international multicenteric survey involving 100 cancer pain control clinicians from 24 countries. The IASP interpreted the result for 1095 patients, that 71.6% of patients had nociceptive somatic pain. Of these, 34.7% of the pain had visceral nociceptive pain; 41.7% of patients had pain syndromes involving bones and joints and 27.8% of peripheral nerve injuries suggesting the need for creation of a written checklist of cancer pain syndromes and pathophysiologies Bone metastasis is the most common cause of chronic pain in cancer patients.[9]

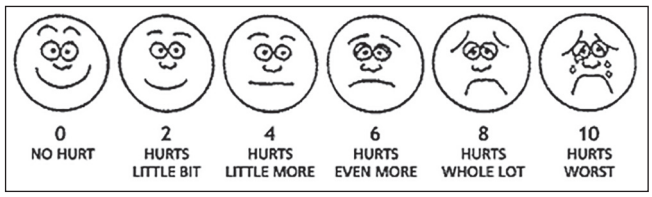

Figure 1: The Wong Baker Scale for assessment of pain in children[6]

Break through Pain

Pain that is over and above the background pain is called as breakthrough pain (BCP). A study has reported that half to two-third patients with chronic cancer pain experience BCP. BCP is unpredictable pain of rapid onset and high intensity with a mean duration of 30 minutes that occurs even after the pain relief medications are being given to treat the background pain. BCP must be managed promptly as the quality of life depends on the overall pain control.[10]

Figure 2 depicts breakthrough pain. BCP is managed by giving 10-20% of the total daily dose of oral morphine as rescue dose. The episodes of BCP may occur spontaneously or occur at the time when wearing off the analgesic effect (end of dose failure) occurs. End of dose failure should be managed by increasing the sustained release opioid dose or decreasing the frequency of drug administration.[11, 12, 13] The current recommendation is to use a sustained release opioid formulation to treat persistent cancer pain and provide the patient with a fast-acting, short-duration analgesic to take when BCP occurs. Whenever possible, the same opioid that is used in sustained release (s/r) form to manage the persistent pain should be prescribed for BCP. For example, s/r morphine is used for the persistent pain, immediate-release morphine should be used for the BCP.[14]

Available pharmacological modalities of CA pain management in India[1]

Nonopioids: Paracetamol, ibuprufen, diclofenac, naproxen, ketorolac, meloxicam, etoricoxib, nimesulide, nalbuprofen, aspirin, indomethacin.

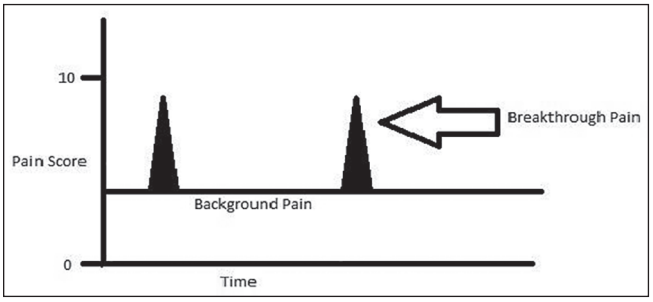

Figure 2: Depiction of Break through Pain

Table 1: Classification of Pain[5]

Classification	Mechanism of action	Symptoms	Pharmacological management
Nociceptive pain	Tissue damage	Cramp, soft tissue pain, bone pain, liver capsule pain	Muscle relaxants NSAIDs±opioids Opioids±NSAIDs, corticosteroids
Neuropathic pain Nerve compression Nerve injury De-afferentation pain Central pain	Stimulation of nervi nervorum Peripheral, CNS injury	Pain in an area of abnormal or absent sensation is always neuropathic Deep ache	Opioid+corticosteroids Opioid; NSAIDs; tricyclic antidepressants antiepileptics; NMDA-receptor-channel blocker; spinal analgesia; TENS
Sympathetically mediated pain	Related to sympathetic nerve trauma	Associated with cutaneous vasodilation, and sweating	Poor response to analgesics and adjuvants

Weak opioids: Tramadol, codeine, dihydrocodiene, dextropropoxyphene (*Dextropropoxyphene has been banned in India*).

Strong opioids: Morphine, buprenorphine, fentanyl (methadone and oxycodone are not available in India).

Adjuvants: Corticosteroids, antidepressants, anticonvulsants, muscle relaxants, antispasmodics, antibiotics, anxiolytics, antiemetics, antibiotics, anxiolytics, sedatives, antacids, Proton pump inhibitors, bisphosphonates

WHO Step ladder for the pain management[1]

Step 1 (The nonopioids ± adjuvants)

Start the medicines but if there is no improvement in 24 h, proceed to step 2.

Treatment may be started with paracetamol 500 mg to 1 g four times a day.

Step 2 (Weak opioid ± step one medication)

Start treatment with a weak opioid eg tramadol or codeine. If step 2 medications are not adequate, proceed to step 3 in 24 h.

Step 3 (Strong opioid ± step one medication)

If step 2 medication is inadequate consider starting oral morphine; 5-10 mg of morphine 4 hourly/six times a day.

If the pain is still not controlled, it needs to be reassessed on a regular basis. Patients' nature of pain might have changed and therefore dosing of the prescribed medicine needs to be changed or adjuvant analgesic needs to be added. The other dimensions of pain, namely, psychosocial, social, spiritual need to be explored and efforts need to be put to reduce these issues.

Dextropropoxephene ban not justified in India

The recent ban by Government of India on Dextropropoxyphene, a step II opioid, one of the least expensive pain relieving medicines has raised concerns for cancer patients, oncologists and palliative care doctors in India who wonder that after the strict narcotic rules, which have already deprived cancer patients of strong opioids, this ban will further add to the problems of effective pain relief for the cancer patients. The government announced this in the Gazette of India on May 23, 2013 due to reporting of 17% of suicidal deaths due to poisoning by Dextropropoxephene in UK. Palliative care experts in India have pointed out that even after the ban the incidence of suicidal deaths have not decreased in UK and this ban is nothing short of a calamity for cancer patients in India.[15]

Table 2 describes the common routes of drug administration of commonly prescribed analgesics in CA pain. IV Paracetamol should be given by infusion over 15 min, and the minimum dose interval should not be less than 4 h (6 h in patients with renal impairment). For rapid effects, iv morphine is rapidly titrated and oral dose is calculated once the pain is controlled by using the ratio of 1:3 or 1:2 for the patients with low (5 mg, every 4 hourly, i.e., 30 mg/day) or high test dose (10 mg, every 4 hourly, i.e., 60 mg/day) respectively. For example, 30 mg test dose × 3 = 90 mg/day is the dose required orally, that is, 15 mg, every 4 hourly.[5]

Transdermal patches of fentanyl should only be used if the patient is having intolerable side effects with morphine or has dysphagia or tablet phobia or renal failure. Transdermal patches of fentanyl should not be used for rapid titration of severe uncontrolled pain as steady state of plasma concentration is achieved after 36-48 h and therefore the patient should use morphine tablets liberally for the first 3 days after applying the patch and if after 48 h the patient still needs rescue tablets of morphine, patch strength should be increased by 25 μg/h.[5] The intravenous fentanyl bolus doses can be used for rapid titration for relief from cancer pain as fentanyl is more lipophilic and can yield quicker relief than intravenous morphine. Intravenous dose of fentanyl is 10% (e.g., 100 μg) of the total intravenous morphine dose (e.g., 100 mg) taken in 24 h, which is rapidly upgraded by 50% in 10 min in the step 2 (e.g., 150 μg) If the pain is not relieved by these efforts step 2 may be repeated and then if pain score is still above >4 other causes of pain must be considered (spiritual, psychological, neuopathic).[21] US Food and Drug Administration advisory panel in 1997 approved the use of fentanyl lollypops for the benefit to cancer patients as it far outweighed the risk that young children would be harmed.[22] Normally 25% of the drug is absorbed directly into the blood stream via the buccal mucosa while 75% is swallowed and then slowly absorbed and undergoes first pass metabolism. Fifty percent of the total dose will reach the bloodstream via both routes available for

Table 2: Common routes of administration and doses of some prescribed analgesic medicines used for CA pain [1,16-20]

Medicine	Route/s of administration	Frequency of administration of medicines	Dose
Step I Paracetamol[16]	Oral/IV	QID	500 mg-1 g (max. 4 g)
Ibubrufen	Oral	TDS	200-400 mg
Diclofenac[17,18]	Oral/IM/rectal suppository/IV	TDS	50-75 mg
			75 mg ampoules (IM) and IV (diluting in 0.9% NS or 5% glucose after buffering with sodium bicarbonate)
Naproxen	PO/suppository	BD	250-500 mg
Ketorolac[19]	Oral/IV/IM/SC	QID	10-30 mg
			15-30 mg (injections)
Tramadol[20]	Oral/IV/IM/SC	QID	50 mg tablets and 100 mg/2 ml injection
			Max. dose 400 mg/day
Morphine	Oral/SC/IV	Six times a day	Start with 5-10 mg and titrate upwards till pain relieved or undesirable side effects appear
Fentanyl	Transdermal patches/lozengess/injections	Every 72 hrs for the patch	Patch strength: 25, 50, 75, 100 μg/h for 3 days
Buprenorphine	Sublingual tablets/transdermal patches/IM/IV	QID(sublingual, im, iv)	0.2-0.6 mg (Sublingual), 5, 10, 20, 35, 70 μg/h (patches) for 4-7 days
			0.3-0.6 mg (im, iv)

pain relief and is considered to treat BCP. The fentanyl lozenges is available in six dosages, measured in micrograms (mcg): 200, 400, 600, 800, 1200, and 1600 mcg, given upto four times a day.[23]

Buprenorphine transdermal patches have an added advantage of long-term antihyperalgesic effects, lack of analgesic tolerance and safety in patients of renal disease (morphine metabolites accumulate in renal disease) in contrast to other opioids, which after long-term use may cause hyperalgesia and tolerance however transdermal patches should not be used to relieve acute pain.[24] Preclinical studies suggest that buprenorphine may be of particular benefit in neuropathic pain.[25] As compared with transdermal fentanyl patch, buprenorphine transdermal patch has a slower rate at which steady state is achieved, adheres better to skin but also causes more erythema.[26,27] The adult dose of buprenorphine injection is 0.3-0.6 mg im/iv at an interval of 6 h.[28] Table 3 describes the side effects and its management caused by opioids.

Continuous subcutaneous infusions

End of life changes generally make the oral route of drug administration impossible for many cancer patients therefore alternative routes like use of continuous subcutaneous route of drug administration needs to be resorted to as it is as effective as the intravenous route and is more safe and cost effective. Additional advantage of continuous subcutaneous infusion (CSI) is that it can be advised for use in home care set up where the patient is managed at home by a visiting nurse. Morphine, fentanyl, and buprenorphine infusions are given to control the pain of terminal cancer patients and a standard practice in palliative medicine.[29-31]

Morphine misconception

The common misconception that opioid analgesics like morphine should be reserved for terminal cancer patients and should be kept as a last option due to chances of addiction needs a reconsideration as use should not be so tight-fisted that the patient loses all hope and trust on the treating physician. Strong opioids need to be given and not always withheld. The side effects of opioids can be avoided if cautious use is done from the beginning. There is also a need to understand that all pains may not be responsive to opioids For example. muscle spasms, abdominal cramps, , raised intracranial pressure psychosocial and spiritual pain, and alternative therapies for management of pain (transelectrical nerve stimulation, cognitive behavioral therapy, heat padding, relaxation techniques, etc.) might need a consideration. Laws provide considerable protection to medical professionals who follow the principles of double effect. The unintended outcome (i.e., death) after a good intention (i.e., administering an opioid to relieve pain) is known as the "double effect." [1,5,32]

Table 3: Specific management of opioid side effects[1]

Side effects with opioids	Management of opioid side effects
Drowsiness	Tolerance will develop in a week. For persistent drowsiness, opioids may be stopped temporarily and other causes (uremia, hypercalcemia) have to be ruled out
Hallucinations or Delirium	Reduce dose of opioids and consider adding haloperidol 2.5-5 mg HS PO/SC
Myoclonus	Opioids in patients of renal failure may cause toxic metabolites to accumulate and cause myoclonus. Treatment consists of parentral rehydration and clonazepam 1-2 mg/24h
Constipation	Stimulant laxatives like bisacodyl 10 mg HS increased to TDS doses if required
Nausea and vomiting	Tolerance develops in a week. Metaclopromide 10 mg TDS or haloperidol 1.5-2.5 mg HS
Pruritis	Ondensetran 8 mg BD, 8 mg iv stat for 3-5 days
Respiratory depression	Rare with oral morphine. If continuous morphine infusion being given, it should be stopped to allow plasma levels to decrease. Naloxone only indicated in severe cases.
Opioid hyperalgesia and allodynia	Usually associated with myoclonus and increase of dose worsens the pain. Alternative opioid or reduction of opioid dose and addition of a coanalgesic may help

Golden rules for adequate analgesia in CA patients.[5]

1. The aim of adequate pain relief is that it should be by the mouth, by the clock and by the ladder.
2. Dose should be individualized and titrated upwards till the pain is relieved or unwanted side effects prevent further dose escalation.
3. Adjuvant analgesics should be used to control pain, undesirable side effects of analgesics, anxiolytics.
4. Most bone, soft tissue, and nerve injury pain may require the combination of NSAIDs and opioids as inflammation may cause peripheral hyperexcitability, which may cause opioids to cause limited pain relief.
5. A pain which is resistant to get relieved must undergo progressive pain relief plan where aim of therapy should be to:
   a. Provide relief at night.
   b. Relief at rest during day.
   c. Relief during movement.
6. In patients undergoing chemotherapy or suffering from thrombocytopenia due to any other reason it is best to use NSAIDS, which have no effect on platelet dysfunction like nimesulide, rofecoxib, meloxicam, etc.[33]
7. Tramadol lowers the seizure potential and should not be used in patients of epilepsy or those taking medications that lower seizure threshold.
8. Strong opioids should be used liberally in patients whose pain is not relieved by other analgesics. Strong opioids do not cause clinically important respiratory depression in patients of pain.[34]
9. When the pain is not relieved by combination of NSAIDs + opioids + adjuvants, the psychosocial dimension of suffering must be explored and managed with behavioral therapies, other nonpharmacological therapies like TENS, acupuncture, palliative and chemotherapy should also be considered.
10. Guidelines must be followed for starting a patient on oral morphine.

Guidelines for starting a patient on opioid analgesics[5]

1. Oral morphine is indicated only when the patient does not respond to the combined use of nonopioid and weak opioid.
2. If shifting from a weak opioid, the starting dose in healthy adult is 5-10 mg, six times a day.
3. The conversion ratios have to be followed when shifting from one strong opioid to another (fentanyl).
4. Patient is also advised to take additional doses in between, if the pain is not getting relieved by the prescribed doses. If the patient requires two or more such doses every day, then the total dose of morphine may be increased by 30-50% every 2-3 days.

5. In patients of renal failure due to accumulation of the metabolite less frequent dosing is preferable, for example, 5-10 mg, four times a day. Transdermanl fentanyl may be preferred in renal failure patients as it does not form any active metabolite.
6. Upward titration of morphine should be stopped when the pain disappears or intolerable side effects appear. Patient must be warned about the initial drowsiness.
7. The hand that prescribes morphine must be vigilant enough to prescribe antiemetics like metaclopromide and laxatives like bisacodyl.
8. Prescription must be clearly explained to patients and regular follow ups be arranged to assess the relief from pain.
9. Pain not relieved by oral morphine will not be relieved by transdermal fentanyl. Transdermal fentanyl is not a preferred agent to relieve acute severe uncontrolled pain. Transdermal fentanyl may be preferred because they cause less nausea and constipation,and are prefered in renal failure and dysphagic patients.
10. Steady state plasma concentrations of fentanyl are achieved in 36-48 h, hence oral morphine may be used liberally for the first 2-3 days. If the pain does not get relieved after 3 days, the dose of fentanyl patch may be increased.
11. Patch should be applied on noninflamed, nonradiated and hairless skin, and the position of the patch be changed every time to give adequate rest the patch area. In febrile patients the rate of absorption might increase and cause toxicity like drowsiness.

Conversion ratio of fentanyl patch/oral morphine[1]

As the potency ratio of fentanyl patch/oral morphine is 100. Dose needs to be adjusted accordingly, for example:

If with oral morphine the total dose is 240 mg/24 h, then 2.4 mg of fentanyl is required in 24 h (240/100).

In the 1-h dose required is 100 μg/h (2.4 mg/24 h; 0.1 mg = 100 μg).

A patch of 100 μg should be chosen for the patient.

Barriers to adequate pain relief

The biggest barrier to adequate analgesia in India is the insensitive attitude that some physicians and patient relatives have toward cancer pain. Some doctors accept pain as an inseparable consequence of the disease and fail to address it as aggressively as they do for the disease *per se Patients may be advised that they will* have to bear the pain, it is a part of disease progression. Cancer pain is one of the most misunderstood, under diagnosed, and under treated/untreated medical problems, particularly in children. Many providers believe that children experience less pain than adults and children are too fragile to receive narcotics. Many children deny pain because of fear of disappointment to the parents and it may not be unusual to find children saying "I say that there is no pain because mom cries when I have pain". Many health care providers misunderstand use of distraction techniques by children to absence of pain.[35]

Stringent narcotic rules

The 1985 Narcotic Drug and Psychotropic Substance act (NDPS) rules have been amended in 1998 by Government of India simplifying morphine licensing for possession and prescription by medical institutions providing palliative care. A few states like Kerala, Karnataka, Madhya Pradesh, Goa, Uttar Pradesh, Arunachal Pradesh, Andhra Pradesh, Tamil Nadu, Orissa, Sikkim, Tripura, Jammu and Kashmir, and Delhi have amended their rules and have given Registered Medical Institution (RMI) status to the hospitals where palliative care is being provided. [36,37] In other states morphine licensing is still a very painful procedure for the institutions trying to provide pain relief to the cancer patients and due to this troublesome procedure of morphine licensing many patients do not get adequate analgesia and die in pain [38]

Conclusion

Most patients with CA have moderate to severe pain during their illness and many fear pain more than death itself. A consensus exists among palliative experts that this difficult to treat pain can be adequately managed if the four dimensions of pain are adequately addressed. Unfortunately many physicians are not sensitive to the screams of the dying cancer patients in India and very few patients die a dignified death. Very few cancer centers in India have separate pain and palliative care units. This review may be considered a request from authors to all the oncologists, cancer centers, state and central government health ministry to incorporate pain, and palliative care education at the level of primary health care centers throughout India as cancer is one of the leading causes of death.

References

1. Nandini V. Management of pain. In: Mathews L, editor. Handbook for certificate course in essentials of palliative care. 4th ed. Calicut: Harvest Printing Services; 2012.
2. Bruera E, Kim HN. Cancer Pain. JAMA 2003;290:2476-9.
3. Strang P. Cancer Pain — A Provoker of emotional, social and existential distress. Acta Oncol 1998;37:641-4.
4. Lemay K, Wilson KG, Beunger U, Jarvis V, Fitzgibbon E, Bhimji K, *et al*. Fear of pain in patients with advanced cancer or in patients with chronic non cancer pain. Clin J Pain 2011;27:116-24.
5. Grossman SA. Undertreatment of Cancer pain: Barriers and remedies. Support Care Cancer 1993;1:74-8.
6. Introducing Palliative Care. Robert Twycross. 4th ed. Radcliffe Medical Press; 2003. p. 190.
7. Wong DL, Hocken Berry EM, Wilson D, Winkelstein ML, Schwartz P. Wong's Essentials of Pediatric Nursing. 6th ed. St.Louis: Mosby, Inc. 2001. p. 1301.
8. Grond S, Zech D, Diefenbach C, Radbruch L, Lehmann KA. Assessment of cancer pain: A prospective evaluation in 2266 cancer patients referred to a pain service. Pain 1999;64:107-14.
9. Merskey H, Bogduk N. Classification of chronic pain. 2nd ed. Seattle: IASP Press; 1994. p. 56-98.
10. Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. Pain 1999;82:263-74.
11. Portenoy RK, Hagen NA. Breakthrough pain: Definition, prevalence and characteristics. Pain 1990;41:273-81.
12. Walsh D, Rivera NI, Davis MP, Lagman R, Legrand SB. Strategies for pain management: Cleveland Clinic Foundation guidelines for opioid dosing for cancer pain. Support Cancer Ther 2004;1:157-64.
13. Hanks GW, Conno F, Cherny N, Hanna M, Kalso E, McQuay HJ, *et al*. Morphine and alternative opioids in cancer pain: The EAPC recommendations. Br J Cancer 2001;84:587-93.
14. Hagen NA, Biondo P, Stiles C. Assessment and management of breakthrough pain in cancer patients: Current approaches and emerging research. Curr Pain Headache Rep 2008;12:241-8.
15. Pasero CL, Portenoy RK, McCaffery M. Opiod analgesics. In: McCaffery M, Pasero CL, editors. Pain: Clinical manual. 2nd ed. St. Louis: Mosby 1999. p. 161-299.

16. Sharma DC. India urged to reverse dextropropoxyphene ban. Lancet Oncol 2013;14:e344.
17. Gray T, Hoffman RS, Bateman DN. Intravenous paracetamol — an international perspective of toxicity. Clin Toxicol (Phila) 2011;29:150-2.
18. Singh R, Deepak B, Baduni N, Vajifdar H. Anaphylactic reaction to intravenous diclofenac. Indian J Crit Care Med 2011;15:37-9. Available from: http://portal.bpfk.gov.my/aeimages/File/Product_Info/poison/Diclofenac_Sodium_Solution_for_Injection.pdf [Last accessed on 2013 Aug 10].
19. Analgesics. Available from: http://www.mayoclinic.com/health/drug-information/DR601483/DSECTION=proper-use [Last accessed on 2013 Aug 12].
20. Joishy SK. Walsh D. The opioid-sparing effects of intravenous ketorolac as an adjuvant analgesic in cancer pain: Application in bone metastases and the opioid bowel syndrome. J Pain Symptom Manage 1998;16:334-9.
21. ;http://www.medicines.org.uk/guides/tramadol%20hydrochloride/pain/tramadol%20100mg~2ml%20solution%20for%20injection%20ampoule [Last accessed on 2013 Aug 11].
22. Guilherme L, Soares L, Martins M, Uchoa R. Intravenous Fentanyl for Cancer Pain: A "Fast Titration". J Pain Symptom Manage 2003;26:876-81.
23. US FDA panel recommends pain killing lollipop. Available from: http://www.nytimes.com/1997/09/18/us/fda-panel-recommends-pain-killing-lollipop.html [Last accessed on 2013 Aug 7].
24. Fentanyl. Available from: http://en.wikipedia.org/wiki/Actiq [Last accessed on 2013 Aug 7].
25. Pergolizzi JV Jr, Mercadante S, Echaburu AV, Van den Eynden B, Fragoso RM, Mordarski S, *et al*. The role of transdermal buprenorphine in the treatment of cancer pain: An expert panel consensus. Euromed Communications meeting. Curr Med Res Opin 2009;25:1517-28.
26. Budd K, Raffa R, editors. Buprenorphine - the unique opioid analgesic. Stuttgart, Germany: Georg Thieme Verlag; 2005. p.134.
27. Schmid-Grendelmeier P, Pokorny R, Gasser UE, Richarz U. A comparison of the skin irritation potential of transdermal fentanyl versus transdermal buprenorphine in middle-aged to elderly healthy volunteers. Curr Med Res Opin 2006;22:501-9.
28. Sittl R, Nuijten M, Nautrup BP. Patterns of dosage changes with transdermal buprenorphine and transdermal fentanyl for the treatment of non cancer and cancer pain: A retrospective data analysis in Germany. Clin Ther 2006;28:1144-54.
29. Buprenorphine injection. Available from: http://www.drugs.com/pro/buprenorphine-injection.html [Last accessed on 2013 Aug 7].
30. Bruera E, Brenneis C, Michaud M, Bacovsky R, Chadwick S, Emeno Al. Use of the subcutaneous route for administration of narcotics in patients with cancer pain. Cancer 1998;62:407-11.
31. Ferris F, Wodinsky H, Kerr I, Sone M, Hume S, Coons C. A cost minimization study of cancer patients requiring a narcotic infusion in hospital and at home. J Clin Epidemiol 1991;44:313-27.
32. Anderson SL, Shreve ST. Continuous subcutaneous infusion of opiates at end-of-life. Ann Pharmacother 2004;38:1015-23.
33. Justad M. Continuous subcutaneous infusion: An efficacious, cost-effective analgesia alternative at the end of life. Home Healthc Nurse 2009;27:140-7.
34. Bennet A. The importance of COX-2 inhibition for aspirin induced asthma. Thorax 2000;55(Suppl 2):S54-6.
35. Richard A, Charles B. Respiratory effects of opioids. International Association for study of pain; 1997. Merck &Co, New jersey.
36. Paris PM. Pain management in the child. Emerg Med Clin North Am 1987;5:699-707.
37. Guidelines for developing Palliative care services. Recommendations of an expert group meeting 17-18 June 2008. Developed under the Government of India and World Health Organisation Collaborative Program. All India Institute of Medical Sciences; 2008-2009. p. 4-6.
38. Mercadante S, Patrizia V, Ferrera P, Casuccio A, Fulfaro F. Rapid titration with intravenous morphine for severe cancer pain and immediate oral conversion. Cancer 2002;95:203-8.

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