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

Raghavendra Ramanjulu, Raghu S Thota[1], Arif Ahmed[2], Parmanand Jain[1], Naveen Salins[3], Sushma Bhatnagar[4], Aparna Chatterjee[1], Dipasri Bhattacharya[5]

Department of Pain and Palliative Care, Cytecare Hospital, Bengaluru, [3]Department of Palliative Medicine and Supportive Care, Manipal Comprehensive Cancer Care Centre, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, [1]Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, [2]Department of Anaesthesia, Critical Care and Pain Management, CK Birla Hospital for Women, Gurugram, Haryana, [4]Department of Onco-anaesthesia and Palliative Medicine, Dr. B. R. A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, [5]Department of Anaesthesiology, Critical Care and Pain, R. G. Kar Medical College, Kolkata, West Bengal, India

Abstract

The Indian Society for Study of Pain (ISSP), Cancer Pain Special Interest Group guidelines on pharmacological management of cancer pain in adults provides a structured, step-wise approach which will help to improve the management of cancer pain and to provide the 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 drafts 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 (IAPC) members. We recommend that analgesics for cancer pain management should follow the World Health Organization three-step analgesic ladder appropriate for the severity of pain. The use of paracetamol and nonsteroidal anti-inflammatory drugs alone or in combination with opioids for mild-to-moderate pain should be used. For mild-to-moderate pain, weak opioids such as tramadol, tapentadol, and codeine can be given in combination with nonopioid analgesics. We recommend morphine as the opioid of first choice for moderate-to-severe cancer pain.

Keywords: Cancer pain management guidelines, cancer pain management, cancer pain Special Interest Group, Indian Association of Palliative Care, Indian Society for Study of Pain, opioids, World Health Organization analgesic ladder

Introduction

Worldwide, low-and middle-income countries are experiencing significant increases in rates of noncommunicable diseases, including cancer.[1] In India, more than one million new cases of cancer are diagnosed each year, and it is estimated that the cancer burden in India will almost double during the coming 20 years.[2] The incidence of pain in advanced stages of cancer approaches 70%–80%.[3] A meta-analysis of epidemiological studies on cancer pain revealed that the pain prevalence rates were 39.3% (95% confidence interval [CI] 33.3–45.3) after curative treatment; 55.0% (95% CI 45.9–64.2) during anticancer treatment; 66.4% (95% CI 58.1–74.7) in advanced, metastatic, or terminal disease and 50.7% (95% CI 37.2–64.1) in all cancer stages.[4] It was also shown that over 38.0% of all cancer patients experienced moderate-to-severe pain (pain score >4/10).[4] In a study done in four regional cancer centers in India, a total of 88% of patients reported experiencing pain for about 7 days, and approximately 60% reported that their worst pain was severe.[5]

Although pain is often the primary presenting symptom of cancer and despite the presence of guidelines and the

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Address for correspondence: Dr. Raghu S Thota, Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Centre, Homi Bhabha National Institute, E Borges Road, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: ragstho24@gmail.com

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availability of opioids, cancer pain still remains undertreated. In a systematic review[6] published in 2014 using the Pain Management Index, approximately one-third patients did not receive appropriate analgesia proportional to their pain intensity, as advised by World Health Organization (WHO) analgesic ladder.

The WHO states that "Drug treatment is the mainstay of cancer pain management."[7] Pain treatment using WHO guidelines provide pain relief in majority of patients, though an effective pain relief may take a long time in one-third of the patients. Some advocate a fourth step of interventional therapies to the ladder and recommend using a flex approach rather than a step-wise approach for optimal pain relief.[8] 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 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 the 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 results of the questionnaire [Appendix V] circulated during the meeting and also was 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.

The pharmacological treatment remains the mainstay of cancer pain management. There are various group of pharmacological agents used for the management. For simplicity, we classify them as:

1. Nonopioid analgesics
2. Opioid analgesics
3. Adjuvant analgesics.

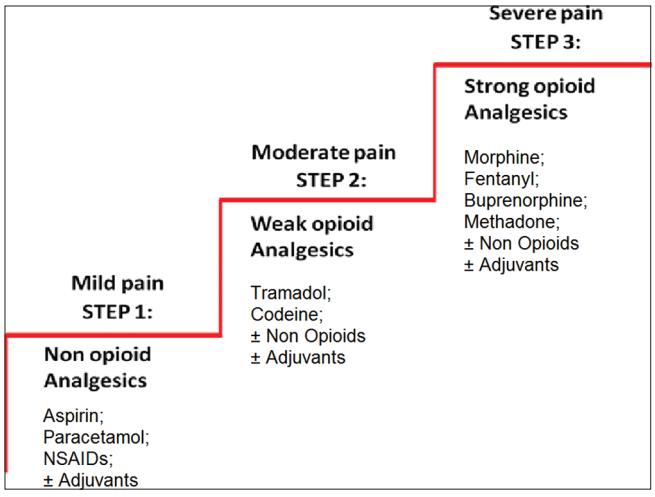

Figure 1: The World Health Organization three-step analgesic ladder

In 1986, a three-step analgesic ladder was launched by the WHO, advocating prompt administration of simple analgesics and oral opioids to control cancer pain.[9]

World Health Organization ladder

The referral point for managing cancer pain often starts with the WHO analgesic stepladder [Figure 1], introduced first in 1986. The sequential original three-step ladder guided the physician in prescribing pain medications based on the magnitude of pain experienced by the patient. The intensity being scored as mild (≤4/10), moderate (5–6/10), and severe (≥7/10).[9,10]

This simple unidirectional guide has been challenged and debated but has remained uncontested in regard to the educational value and the relief it has brought since its worldwide introduction to many who suffered pain.[11] The adaptation of the WHO analgesic ladder integrated a fourth step to the ladder, as well as, its use in a bidirectional manner.[8] The ascending pathway allowed for use in chronic pain and cancer pain, while the descending pathway allowed for management of acute severe pain, uncontrolled chronic pain, and severe breakthrough pain. The ascending or descending speed directed by the intensity of pain experienced.[8] Evidence recommends that interventions incorporated into the fourth step may be useful earlier in disease trajectory rather than for when pain refractory to pharmacological management.[12]

The WHO analgesic stepladder[9] recommends the use of nonopioid analgesics at all the steps. These nonopioid analgesics for the first step for mild pain-paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) (Step 1). Mild-to-moderate pain (Step 2) use of weak opioids is recommended. Strong opioids are the mainstay for moderate-to-severe pain (Step 3). There is a limited availability of different formulations of opioids in India. We have morphine tablet and injection formulations, buprenorphine transdermal/injection/tablet formulations, fentanyl transdermal/injection/lollipop formulations, methadone as syrup formulations. Oxycodone and hydromorphone formulations are not available in India.

Management of mild pain

Nonopioid analgesics – Step 1 of three-step World Health Organization analgesic ladder

Paracetamol and NSAIDs are the analgesics used for the management of cancer pain through any stage of the three-step WHO analgesic ladder. They are used alone, as a combination with adjuvants or in combination with opioids. Both medications have a "ceiling effect" or maximum therapeutic dose beyond which, the risk of toxicity increases with no additional analgesic benefits.

Paracetamol

A Cochrane review in 2017, found no evidence of using paracetamol alone. In regard to the opioid-sparing effect

of paracetamol, it stated that although reduction in drug burden from large dosages of opioids was possible, there is no evidence to support the same. There is no high-quality evidence to support or refute the use of paracetamol alone or in combination with opioids for the first two steps of the three-step WHO cancer pain ladder. The authors did find randomized controlled trials (RCTs), but the GRADE assessment of evidence quality was very low for all outcomes, because studies were at high risk of bias from several sources.[13]

Nonsteroidal anti-inflammatory drugs

The anti-inflammatory and analgesic effects of NSAIDs are based on the suppression of the COX-1 and COX-2 enzymes. By blocking the COX enzymes and prostaglandins, vasodilation is reduced, and inflammation is relieved causing reduction of pain. Nonselective NSAIDs such as ibuprofen, diclofenac, indomethacin, naproxen, and piroxicam block COX-1 and COX-2 enzymes to various degrees. Selective COX-2 inhibiting NSAIDs such as celecoxib and etoricoxib selectively inhibit the COX-2 enzyme. COX-1 enzyme is responsible for gastric mucosal protection, and hence blockade of this leads to the gastrointestinal side effects of NSAIDs. The others include antiplatelet, cardiovascular, renal, and hepatotoxic side effects.[14,15]

A Cochrane review held in 2017 identified 11 studies that looked into the effects of NSAIDs on their own, comparative studies of various NSAIDs and NSAIDs with opioids. Moderate or severe cancer pain was reduced to no worse than mild pain in 26%–51% of patients using any NSAIDs, after 1 or 2 weeks in 4 of the 11 studies. Thus, based on this review, we have no high-quality evidence to support or refute the use of NSAIDs alone or in combination with opioids for the three steps of the three-step WHO cancer pain ladder.[16]

Depending on the cause of pain, topical NSAID gel or patches can be tried for analgesia.

Management of mild-to-moderate pain

Weak opioid analgesics – Step 2 of three-step World Health Organization analgesic ladder

The Step 2 in WHO Ladder is used to manage moderate cancer pain.

Tramadol, codeine, and tapentadol are the drugs in Step 2.

Tramadol

Tramadol acts as a μ-opioid agonist, and a serotonin and noradrenaline reuptake inhibitor. Its effect on serotonin reuptake can potentially lead to serotonergic syndrome, especially in the elderly and with polypharmacy (e.g. metoclopramide, ondansetron, antidepressants). One RCT provided direct comparative data for the step 2 opioids, and it showed no difference in efficacy between tramadol, codeine plus paracetamol, and hydrocodone plus paracetamol, although tramadol was associated with more side effects.[17]

Codeine

Codeine exerts its analgesic effect when metabolized to morphine mainly via the CYP2D6 enzyme. There are four phenotypic categories of CYP2D6 polymorphisms-ultra rapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. No significant difference was found between the effectiveness of nonopioid analgesics and nonopioids in combination with weak opioids in a meta-analysis.[18,19] The available evidence suggests that codeine is more effective against cancer pain in adults than placebo, but with increased risk of nausea, vomiting, and constipation.[20]

Step 2 weak opioids have a therapeutic ceiling effect and increased incidence of side effects. There is no evidence that in moderate pain initiation of step 2 drugs alone improve pain. European Association for Palliative Care recommends the use of low-dose step 3 opioids such as morphine, oxycodone, and hydromorphone in management of moderate cancer pain in opioid-naïve patients.[21] Oxycodone and hydromorphone are not available in India. In a Cochrane review in 2017 on tramadol, the authors have suggested that there is limited, very-low-quality evidence from RCTs that tramadol produced pain relief in some adults with pain due to cancer.[22] The quality of evidence is very low to say that tramadol is not as effective as morphine.

Tapentadol

Tapentadol is a novel, centrally-acting analgesic agent with two mechanisms of action: μ opioid receptor agonism and norepinephrine reuptake inhibition. Tapentadol has been developed for the management of moderate-to-severe chronic pain. The moderate affinity at the μ receptor and the opioid-sparing effect of inhibition of norepinephrine reuptake suggest that tapentadol should produce fewer opioid-related adverse effects than typical μ agonists.[23] Tapentadol, when used at doses equivalent to the step 3 of the analgesic ladder (≥60 mg of oral morphine equivalents) in opioid-tolerant patients with cancer pain, or after titration starting with step 2 doses (<200 mg/day), was well tolerated and effective and could be used for the management of moderate-to-severe cancer pain.[24] In a Cochrane review, the authors concluded that information from RCTs on the effectiveness and tolerability of tapentadol was limited, pain relief, and adverse events were comparable between the tapentadol and morphine and oxycodone groups.[25]

Management of moderate-to-severe pain

Step 3 of the World Health Organization three-step analgesic ladder

Strong opioids are the mainstay of management of moderate-to-severe cancer-related pain. Morphine continues to be the most widely available and prescribed opioid although other opioids do exist.

A Cochrane review of all step 3 opioids showed that the quality of evidence around the use of opioids for cancer pain is low. Ninety-five percentages of patients with moderate-to-severe pain, however, did report decrease in pain by 14 days. Adverse events were reported to be common, but withdrawals due to adverse events uncommon. Oral morphine is still considered

as the gold standard for treating moderate-to-severe cancer pain.[26]

Morphine

Morphine acts on the μ receptors (subdivided into μ1, μ2, and μ3). Morphine is primarily metabolized in the liver by the cytochrome P450 CYP3A4 enzyme to M3G and M6G. In humans, approximately 60% of a morphine dose is converted to M3G and 10% to M6G. M6G contributes significantly to the analgesic potency of oral morphine, while M3G is neuroexcitatory and contributes to the adverse effects of morphine.[27]

In a Cochrane review, all formulations of morphine were compared with each other and other opioids. It was concluded that most patients will achieve a high level of pain relief within at least 2 weeks. A small proportion of participants did not achieve adequate analgesia with morphine and about 6% of participants discontinued treatment with morphine because of intolerable adverse events.[28]

Oral route is the preferred route of administration. Intravenous or subcutaneous route of administered is advised only when rapid control of pain is needed.

Methadone

Methadone a synthetic opioid is a potent agonist at the μ-opioid and delta-opioid receptors. Methadone has also been demonstrated in animal studies to have antagonist activity at the N-methyl-D-aspartate receptor, resulting in interest in management of neuropathic pain syndromes.[29]

A racemic mixture of two isomers-levorotatory (L) methadone and dextrorotatory (D) methadone, with L-methadone is 8–50 times being more potent than D-methadone and responsible for its analgesic properties. After oral administration, it reaches a measurable plasma level in 30 min.

The peak plasma levels are achieved in 4 h and begin to decline 24 h after dosing. Oral bioavailability is high, generally over 85%.

Particular concern is the potential for prolongation of the QT interval (a measure of cardiac function) resulting in the potentially fatal arrhythmia called torsade de pointes.[30,31] The incidence is higher in doses higher than 100 mg a day.

Methadone's properties of high oral bioavailability, rapid onset of analgesic effect, long half-life (resulting in infrequent dosing schedules), lack of active metabolites, and low cost are positive factors for use in the management of pain in cancer patients.

Elimination of methadone is mediated by hepatic oxidative biotransformation, urinary, and fecal clearance. Renal impairment is not thought to impair clearance hence methadone is useful in the management of pain in patients with renal failure.[32] However, patients should be monitored closely for signs of drug toxicity.

In a Cochrane review, in 2017, based on low-quality evidence, methadone was found to have equianalgesic potency, when compared with morphine.[33]

A pain and palliative care specialist needs to be consulted if one is unfamiliar with methadone prescription and monitoring.

Transdermal opioids

Fentanyl

Fentanyl is a strong opioid about 100 times more potent than morphine. It is lipophilic and exhibits strong protein-binding property. It has a large volume of distribution and its clearance relatively high. The inactive metabolites, and approximately 10% of the intact molecule, are mainly excreted by the kidneys.[34]

When administered intravenously, fentanyl is rapidly distributed from plasma into highly vascularized compartments. Following this, redistribution to muscle and fat tissue occurs. Elimination half time is highly variable due to the redistribution.[35]

Fentanyl is a synthetic opioid that acts at the mu opioid receptor. It takes 8–16 h before the full effect of transdermal fentanyl is observed, and steady state is not observed until after two to four applications of the "72-h" patches.[36] When used as a transdermal patch, fentanyl absorption occurs first into the cutaneous microcirculation, before entering the systemic circulation. Factors such as location of the patch applied, hypertrichosis, hyperhidrosis, and factors that could increase the body temperature to >40°C, can affect the absorption of fentanyl from the patch.[37]

The rapid-onset fentanyl products are absorbed by the highly vascularized oral mucosa and nasal membranes before entering the systemic circulation. In cancer patients, only a couple of studies have looked into whether mucositis or xerostomia affects the absorption. The studies have only included Grade 1-2 mucositis. This study of 13 patients did not find statistically significant differences in absorption.[38]

In cases of rhinitis/epistaxis and use of oxymetazoline nasal sprays, can cause a 50% decrease in absorption of fentanyl, postulated as due to vasoconstriction that occurs.[39]

In drug interactions, most strong CYP3A4 inhibitors significantly increased systemic fentanyl exposure and CYP3A4 inducers significantly decreased systemic fentanyl exposure, hence careful observation is required when using these drugs, while fentanyl infusion is ongoing.[35]

Pharmacogenetics also plays a vital role in the pharmacokinetics and pharmacodynamics of fentanyl metabolism.[35]

Buprenorphine

Buprenorphine is a semi-synthetic partial μ-opioid receptor agonist, with agonistic activity on κ-and δ-opioid receptors. It binds to receptors with high affinity and has slow dissociation, thus exhibiting a longer duration of analgesic action. Buprenorphine is available as parenteral, sublingual, and transdermal formulations. Buprenorphine patches are available as 7-day patches mainly, but 3–4 day patches are also available. Transdermal buprenorphine is recommended in patients with renal impairment as, due to its pharmacokinetic profile, buprenorphine does not accumulate in renal failure

Table 1: Summary of recommendations

Recommendations	Level of evidence
Analgesics for cancer pain management should follow the WHO 3-step analgesic ladder appropriate for the severity of pain (Grade B)	IIa
The use of paracetamol alone or in combination with opioids for mild to moderate pain has Grade B recommendation	IIa
The use of NSAIDs alone or in combination with opioids for mild to moderate pain has Grade B recommendation	IIa
For mild to moderate pain, weak opioids such as tramadol, tapentadol and codeine can be given in combination with nonopioid analgesics (Grade B)	Ia/IIa/IIb
As an alternative to weak opioids, low doses of strong opioids could be an option but is not included in WHO guidance (Grade B)	IIa
The opioid of first choice for moderate to severe cancer pain is oral morphine (Grade A)	I
When opioid requirements are stable, transdermal fentanyl should be considered for use (Grade D)	V
In patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 mL/min), fentanyl and buprenorphine (via transdermal and intravenous route) are the safest opioids (Grade B)	IIb
Buprenorphine should be considered as a fourth line drug compared to standard medications for cancer pain (Grade A)	Ia

WHO: World Health Organization, NSAIDs: Nonsteroidal anti-inflammatory drugs

and is not removed by haemodialysis.[40] As per Cochrane review,[40] it might be considered as a fourth-line option compared to the standard therapies such as morphine, oxycodone, and fentanyl.

Conclusion

The ISSP Cancer Pain Special Interest Group (SIG) guidelines on pharmacological management of cancer pain in adults emphasize the importance of the WHO three-step analgesic ladder. The most important aspect of these guidelines is recommendation of oral morphine as the first choice for moderate-to-severe cancer pain. Here, we also emphasize the use of transdermal buprenorphine as a fourth-line drug compared to standard medications for cancer pain [Table 1].

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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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Miranda JJ, Kinra S, Casas JP, Davey Smith G, Ebrahim S. Non-communicable diseases in low- and middle-income countries: Context, determinants and health policy. Trop Med Int Health 2008;13:1225-34.
2. Mallath MK, Taylor DG, Badwe RA, Rath GK, Shanta V, Pramesh CS, *et al*. The growing burden of cancer in India: Epidemiology and social context. Lancet Oncol 2014;15:e205-12.
3. Saini S, Bhatnagar S. Cancer pain management in developing countries. Indian J Palliat Care 2016;22:373-7.
4. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: Systematic review and meta-analysis. J Pain Symptom Manage 2016;51:1070-90.e9.
5. Doyle KE, El Nakib SK, Rajagopal MR, Babu S, Joshi G, Kumarasamy V, *et al*. Predictors and prevalence of pain and its management in four regional cancer hospitals in India. J Glob Oncol 2018;4:1-9.
6. Greco MT, Roberto A, Corli O, Deandrea S, Bandieri E, Cavuto S, *et al*. Quality of cancer pain management: An update of a systematic review of undertreatment of patients with cancer. J Clin Oncol 2014;32:4149-54.
7. World Health Organization. Cancer Pain Relief with a Guide to Opioid Availability. 2nd ed. Geneva: World Health Organization; 1996.
8. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician 2010;56:514-7, e202-5.
9. World Health Organization Staff, World Health Organization. Cancer Pain Relief: With a Guide to Opioid Availability. World Health Organization; 1996.
10. Li KK, Harris K, Hadi S, Chow E. What should be the optimal cut points for mild, moderate, and severe pain? J Palliat Med 2007;10:1338-46.
11. Azevedo São Leão Ferreira K, Kimura M, Jacobsen Teixeira M. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? Support Care Cancer 2006;14:1086-93.
12. Miguel R. Interventional treatment of cancer pain: The fourth step in the World Health Organization analgesic ladder? Cancer Control 2000;7:149-56.
13. Wiffen PJ, Derry S, Moore RA, McNicol ED, Bell RF, Carr DB, *et al*. Oral paracetamol (acetaminophen) for cancer pain. Cochrane Database Syst Rev 2017;7:CD012637.

14. Dwivedi AK, Gurjar V, Kumar S, Singh N. Molecular basis for nonspecificity of nonsteroidal anti-inflammatory drugs (NSAIDs). Drug Discov Today 2015;20:863-73.
15. Altman R, Bosch B, Brune K, Patrignani P, Young C. Advances in NSAID development: Evolution of diclofenac products using pharmaceutical technology. Drugs 2015;75:859-77.
16. Derry S, Wiffen PJ, Moore RA, McNicol ED, Bell RF, Carr DB, *et al*. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. Cochrane Database Syst Rev 2017;7:CD012638.
17. Rodriguez RF, Bravo LE, Castro F, Montoya O, Castillo JM, Castillo MP, *et al*. Incidence of weak opioids adverse events in the management of cancer pain: A double-blind comparative trial. J Palliat Med 2007;10:56-60.
18. Eisenberg E, Berkey CS, Carr DB, Mosteller F, Chalmers TC. Efficacy and safety of nonsteroidal antiinflammatory drugs for cancer pain: A meta-analysis. J Clin Oncol 1994;12:2756-65.
19. Management of cancer pain evidence report technology assessment: Number 35--management of cancer pain summary. J Pain Palliat Care Pharmacother 2002;16:91-102.
20. Larkin PJ, Cherny NI, La Carpia D, Guglielmo M, Ostgathe C, Scotté F, *et al*. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2018;29:iv111-25.
21. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, *et al*. Use of opioid analgesics in the treatment of cancer pain: Evidence-based recommendations from the EAPC. Lancet Oncol 2012;13:e58-68.
22. Wiffen PJ, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. Cochrane Database Syst Rev 2017;5:CD012508.
23. Mercadante S, Porzio G, Aielli F, Adile C, Verna L, Ficorella C, *et al*. Opioid switching from and to tapentadol extended release in cancer patients: Conversion ratio with other opioids. Curr Med Res Opin 2013;29:661-6.
24. Mercadante S. The role of tapentadol as a strong opioid in cancer pain management: A systematic and critical review. Curr Med Res Opin 2017;33:1965-9.
25. Wiffen PJ, Derry S, Naessens K, Bell RF. Oral tapentadol for cancer pain. Cochrane Database Syst Rev 2015;9:CD011460.
26. Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain – An overview of Cochrane reviews. Cochrane Database Syst Rev 2017;7:CD012592.
27. Smith HS. The metabolism of opioid agents and the clinical impact of their active metabolites. Clin J Pain 2011;27:824-38.
28. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. Cochrane Database Syst Rev 2016;4:CD003868.
29. Davis MP, Walsh D. Methadone for relief of cancer pain: A review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. Support Care Cancer 2001;9:73-83.
30. Cruciani RA. Methadone: To ECG or not to ECG.That is still the question. J Pain Symptom Manage 2008;36:545-52.
31. van den Beuken-van Everdingen MH, Geurts JW, Patijn J. Prolonged QT interval by methadone: Relevance for daily practice? A prospective study in patients with cancer and noncancer pain. J Opioid Manag 2013;9:263-7.
32. Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, *et al*. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018;29:iv166-91.
33. Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. Cochrane Database Syst Rev 2017;2:CD003971.
34. Oosten AW, Abrantes JA, Jönsson S, de Bruijn P, Kuip EJ, Falcão A, *et al*. Treatment with subcutaneous and transdermal fentanyl: Results from a population pharmacokinetic study in cancer patients. Eur J Clin Pharmacol 2016;72:459-67.
35. Kuip EJ, Zandvliet ML, Koolen SL, Mathijssen RH, van der Rijt CC. A review of factors explaining variability in fentanyl pharmacokinetics; focus on implications for cancer patients. Br J Clin Pharmacol 2017;83:294-313.
36. Wiffen PJ. Systematic reviews published in the October 2016 issue of the Cochrane Library. J Pain Palliat Care Pharmacother 2017;31:71-2.
37. Hao J, Ghosh P, Li SK, Newman B, Kasting GB, Raney SG. Heat effects on drug delivery across human skin. Expert Opin Drug Deliv 2016;13:755-68.
38. Kuip EJ, Oldenmenger WH, Oomen-de Hoop E, Verduijn GM, Thijs-Visser MF, de Bruijn P, *et al*. Pharmacokinetics of sublingually delivered fentanyl in head and neck cancer patients treated with curatively aimed chemo or bioradiotherapy. Cancers (Basel) 2018;10:445.
39. Winiarczyk K, Knetki-Wróblewska M. Breakthrough pain in cancer patients. Oncol Clin Pract 2016;12:1-7.
40. Schmidt-Hansen M, Bromham N, Taubert M, Arnold S, Hilgart JS. Buprenorphine for treating cancer pain. Cochrane Database Syst Rev 2015;3:CD009596.

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?