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

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

Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, [1]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, [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 (SIG) guidelines on pharmacological management of cancer pain in adults provide a structured, stepwise 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 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. We recommend that analgesics for cancer pain management should follow the World Health Organization 3-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 the first choice for moderate-to-severe cancer pain. Sustained-release formulations can be started 12 hourly, once the effective 24 h dose with immediate-release morphine is established. Opioid switch or rotation should be considered if there is inadequate analgesia or intolerable side effects. For opioid-induced respiratory depression, μ receptor antagonists (e.g. naloxone) must be used promptly. 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 use of ketamine in cancer neuropathic pain, but with no beneficial effect, thus, it is not recommended.

Keywords: Cancer pain management guidelines, cancer pain management, cancer pain special interest group, Indian Association of Palliative Care, Indian Society for Study of Pain, methadone, opioids, side effects of 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.

Access this article online

Quick Response Code:

Website: www.jpalliativecare.com

DOI: 10.4103/0973-1075.285693

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

How to cite this article: Thota RS, Ramanjulu R, Ahmed A, Jain P, Salins N, Bhatnagar S, *et al*. Indian society for study of pain, cancer pain special interest group guidelines on pharmacological management of cancer pain (Part II). Indian J Palliat Care 2020;26:180-90.

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

The WHO states that "drug treatment is the mainstay of cancer pain management."[7] Pain treatment using the WHO guidelines provides pain relief in majority of patients, though 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 stepwise 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 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 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, following extensive discussion among the committee members and considering the results of the questionnaire [Appendix V] which were circulated during the meeting and were also made available on the ISSP website and circulated by e-mail to all the ISSP and Indian Association of Palliative Care (IAPC) members.

Prescribing and titration of opioids

Prescribing analgesics alone does not ensure that the patient achieves pain relief – a comprehensive approach is essential. Oral morphine is the preferred drug of choice for the management of moderate-to-severe cancer pain.

Initiation of therapy

History

A detailed history of patient, his/her disease status, social background, habits, and other medication are necessary.

- Name
- Age/Sex
- Education
- Profession – occupation Address
- Contact number
- E-mail address
- Name of caregiver and relationship: Diagnosis
- Stage of the disease
- Addiction: Tobacco/alcohol/other.
  - How much
  - Cessation: Yes/no since how long?
  - Willing to stop using? Yes/No.
- Family History – Staying alone/Family – Joint/nuclear family
- Who will give medicine – Self-administration/Name of caregiver
- History of opioid/drug addiction: History of hypothyroidism
- History of psychiatry illness
- Any prescription from other sources.

One can use various "Opioid Tools" mentioned in the literature: CAGE–AID Questionnaire,[9] Opioid Risk Tool,[10] Dire Score (D – Diagnosis, I – Intractability of Pain, R – Risk factors, E – Efficacy),[11] Drug Abuse Screening Test,[12] and Screener and opioid Assessment for Patients with Pain-Revised.[13] Choose the tool/questionnaire which is brief and should not take more than 1 min of time.

Consent of patient or caregiver (if patient is not in condition to give consent) is needed for check of urinary drug testing in the future. Consent should also mention that patient will not procure opioids from another provider[14] [Appendix VI – Consent form].

Who can prescribe opioids?

A major barrier to access to morphine and similar opioid medications was overcome by:

a. Amendment of the Narcotic Drugs and Psychotropic Substances (NDPS) Act in 2014 and the relevant NDPS rules for essential narcotic drugs (ENDs) were announced by the Government of India in May 2015.[15] As per the NDPS Act (Amendment) 2015, any registered medical practitioner (RMP) can prescribe opioids. "RMP" means any person registered as a medical practitioner under the Indian Medical Council Act, 1956 or under any law for the registration of medical practitioner for the time being in force or registered as a dentist under the Dentists Act, 1948 or under any law for the registration of dentists for the time being in force and has undergone training in either one of the following courses:
   i. Training in pain relief and palliative care for prescription of ENDs
   ii. Opioid substitution therapy for prescription of ENDs for the treatment of opioid dependence.

How to write opioid prescription?

The prescription should be written in CAPITAL LETTERS,

with generic name of the opioid prescribed. It should have exact number of tablets/injection/patches to be dispatched with timings and route of the drug to be taken. The prescription should be given in three copies: one to be retained by the prescribing author, one to be given to the pharmacist, and one to be carried by the patient. The RMP should sign at the end of the prescription and write his/her Medical Council Registration number.

e.g. TABLET MORPHINE IMMEDIATE RELEASE (IR) 10 mg, 1 tablet 4 hourly

1. __ 1 __ 1 __ 1__ 1 or 2.×30 days=180 tablets

(7am) (11am) (3pm) (7pm) (11pm)

TABLET BISACODYL 5 mg, 2 tablets HS.×30 days = 60 tablets

How much opioid can be given during each visit of patient?

Each institute or department can have their own policy regarding safe prescription of opioids. The distance patient has to travel; the type and severity of pain are the factors to be considered before prescribing the opioids.

Communication with the patient/caregiver before starting opioids

It is very important to communicate with the patient and/or caregiver before starting opioids. A well-informed and educated patient will adhere to the treatment and will be benefited by the drug. Following are the salient features of the patient–doctor communication before prescribing the opioids.

- Inform about around the clock (ATC) medication instead of PRN medication. One can give specific timings to take tablets. E.g., tablet morphine IR is to be taken 4 hourly, orally. One can set the timings of taking this tablet as 7 am, 11 am, 3 pm, 7 pm, and 11 pm (two doses at bed-time)
- Inform about side effects and how to deal with it. It is a rule to prescribe laxatives (stimulant and/or softener) with oral morphine. Patient is also explained necessary changes in diet and liquid intake
- Drug to be kept in safe place, away from children
- Patient can be given a card to keep the record of tablets used
- Patient may be asked to bring empty wrappers and remaining stock of medicine to keep a check on misuse of opioids
- Patient should be asked to come for follow-up before the opioids are completely exhausted.

How to keep a check on opioid abuse/misuse?

This requires appropriate communication with the patient and/or caregiver. Following steps on each follow-up visit of patient should be carried out.

- Check the remaining stock of opioids by pill count, checking of wrappers, and history of amount of medicines consumed. Is there an inadvertent increase in dose? Assess the pain and disease status on every visit
- Check if patient is getting opioids from other physicians
- Check with pharmacist about amount of drug dispensed
- Is patient accompanied by different caregiver every time?

How to start the treatment?

In opioid-naïve patients, morphine or any opioid should be initiated in the lowest dose.[1] The initial dose to start with is oral morphine IR 5 mg every 4 hourly in opioidnaïve patients or 10 mg every 4 hourly in patients already on Step 2 of the WHO ladder therapy.[2] In elderly patients, a dose of 2.5 mg oral morphine IR every 4–6 hourly had shown effective pain relief.[1] For patients receiving IR morphine every 4 hourly, a double dose at bedtime may be recommended for convenience based on consensus to prevent being woken up by pain at night, which is also concluded by a randomized controlled trial.[3] In patients presenting with severe cancer pain, parenteral titration of opioids can be performed, for quicker onset of analgesia. Intravenous (IV) morphine titration provides faster onset of analgesia compared to oral morphine titration.[4] IV morphine should be given in areas with monitoring of patients' vital signs (including heart rate, blood pressure, oxygen saturation, and respiratory rate) and pain relief before, during, and after morphine administration.[5] Refer to algorithmic protocol for acute pain crisis IV morphine titration, Pain Control in Emergency (Rapid Intravenous Morphine Titration) [Appendix VII].

Maintenance of opioid therapy

Regular dosing of opioid therapy ATC is recommended in patients with chronic cancer pain. Patients on oral IR morphine should always receive a regular 4 hourly dose to maintain continuous analgesia.[6] Once the effective 24 h dose is established, and patient's pain is stable, the regimen may be converted to a 12 hourly sustained-release (SR) formulation of the equivalent 24-h IR morphine dose (e.g. if a patient needs a total of 60 mg of IR morphine in 24 h, then we can give him 30 mg of SR morphine in 12 hourly basis). Patient is advised to take morphine IR dose for breakthrough pain (BTP). The dose of morphine is increased in increments of 5–10 mg, if pain is not controlled. A systematic review on oral morphine for cancer pain found that there were no differences in efficacy between IR and SR morphine.[7] A combination of IR and SR preparations could be used to appropriately manage pain tailoring to individual patients' requirements and attitudes.

Follow-up

At each visit, the "4A"s[16] are assessed and documented, as is a fifth A, affect – how the patient feels.

- Analgesia – "On a scale of zero to ten, how much pain do you have today?"
- Activities of daily living – How often and how long do you go out to market or just walk, etc.
- Adverse effects – How's constipation? Any sedation? etc.
- Aberrant behaviours – Document that the patient wants an early refill because she's going on vacation, or has more pain, etc., Anything out of the usual pattern.

Breakthrough pain

Breakthrough cancer pain (BTcP) is a common challenging problem that leads to a decreased quality of life and an increased utilization of healthcare services. The Association for Palliative Medicine of Great Britain and Ireland definition of BTP is "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger,

despite relatively stable and adequately controlled background pain."[8] Based on a systematic review,[17] the prevalence of BTcP varied between 39% and 80%. The Alberta BTP Assessment Tool (ABPAT) resulted to be a well-accepted tool for BTP assessment and characterization in a relatively large cohort of cancer patients.[18]

Standard prescribing for BTcP is to use the same opioid for the management of background pain and BTP as modified-release and IR formulations, respectively.

Oral morphine has been the conventional prescription for BTcP. Limitations in terms of time to onset of action result in delayed or ineffective analgesia and dissatisfaction of pain relief. Different formulations have been developed to provide fast pain relief with fentanyl by non-invasive routes: oral, transmucosal buccal tablet, sublingual tablet, buccal soluble film, and sublingual and intranasal spray.[19] The evidence on pharmacological treatment of BTP is limited and involves mainly oral transmucosal fentanyl citrate (OTFC).[20,21]

In India, OTFC is available in a 200 mcg formulation. The patient is advised to roll it against the inside of the cheek rather than suck the lollipop, till they have adequate pain relief and to discard the remaining drug. The commonly accepted ratio of the breakthrough dose to the ATC medication is 1:6, i. e., equivalent to the 4 hourly opioid doses, but in renal impairment, doses as low as 1/12 of the 24-h dose can be used. This "rescue" dose may be given as often as required (up to 1 hourly). The ATC dose may then be adjusted taking into account the total amount of rescue morphine taken in the last 24 h.[6]

Opioid rotation or opioid switching

The term opioid rotation describes the change from one drug ("first-line opioid") to another ("second-line opioid") owing to intolerable adverse events accompanying adequate analgesia or to increasing side effects when the opioid dose is increased because of inadequate pain relief.[22,23] In all of the studies, pain control was achieved for 14 days after each rotation, and in most of them, the dose of the new drug introduced in each rotation needed to be increased above the dose initially, as calculated from analgesic ratio, except methadone. There was no significant decrease in frequency of side effects, but patients were satisfied with opioid rotation. No particular opioid drug was found to be best suited.[24]

The most common opioid switch in India is transdermal fentanyl followed by transdermal buprenorphine. When switching to transdermal fentanyl, there is a lag time between application of the patch and onset of analgesia due to the pharmacokinetics of the transdermal preparation.[25] Regular 4-hourly oral opioids should therefore be continued for 12 h after application of the patch. Similarly, when converting from SR opioid preparations, the patch should be applied when the last dose of SR opioid preparation is taken. A systematic review[26] on comparison of transdermal fentanyl with SR morphine showed similar efficacy in pain control, but showed less constipation and laxative consumption ($P < 0.001$), increased patient preference ($P = 0.014$) but significantly higher cost ($P = 0.0001$) in patients with moderate-to-severe cancer pain with transdermal fentanyl.

For patients who cannot swallow, those with nausea and vomiting, or those at the end of life who are unable to take oral medication because of weakness or debility, parenteral opioid administration should be considered.[27,28]

Opioid equianalgesic doses

Although conversion tables are available, there are no universally accepted guidelines for equianalgesic conversion; thus, they must be used with caution. Tables of equianalgesic doses should be considered no more than a rough guide for determining the dose of the new drug.[24] A common practice is to reduce the initial converted dose by 25%–50% due to incomplete cross-tolerance.[25,29,30]

Table 1 shows conversion[25,28] of commonly used opioids in India, specific for patients in whom analgesia from the previous opioid is satisfactory.

Management of opioid side effects

Opioid analgesics are associated with a number of adverse effects. Most of the adverse effects generally improve over time, except for constipation. Adverse effects should be anticipated and managed appropriately in a timely manner. Patients should be educated about the side effects and management of these side effects. Common side effects are constipation, nausea and vomiting, delirium, pruritus, central nervous system toxicities such as motor and cognitive impairment and confusion, hallucination, somnolence, sedation, myoclonic jerks, and rarely respiratory depression. Opioid-induced hyperalgesia could develop in patients on long-term opioids and should be identified early to optimize pain management.

Nonpharmacological interventions to maximize and optimize the opioid levels and treat their side effects are essential. It is

Table 1: Dose conversion of commonly used opioids

Opioids	Analgesic ratio
Oral morphine to TD fentanyl*	100:1 (multiplication factor is 10)[@]
Oral morphine to TD buprenorphine[#]	75:1 (multiplication factor is 13.3)
Oral codeine to oral morphine	10:1
Oral tramadol to oral morphine	5:1
Oral morphine to oral methadone[†]	
Oral morphine dose 30-90 mg	4:1
Oral morphine dose 91-300 mg	8:1
Oral morphine dose >300 mg	12:1

*Example: 60 mg oral morphine to 25 µg/h TD fentanyl (multiplication factor is 10 to get mcg/24 h dose), [#]Example: 60 mg oral morphine to 35 µg/h TD buprenorphine (multiplication factor is 13.33 to get mcg/24 h dose), [@]Means: Morphine: Fentanyl ratio is 100:1, which means 1 mg of morphine is equivalent to 0.01 mg of IV fentanyl. This is equivalent to 10 mcg of fentanyl. So if a patient needs 60 mg of morphine in 24 h, multiplying 60 with 10 gives us 600 mcg in 24 h. Dividing 600 by 24 gives 25 mcg/h dose of TD fentanyl, [†]The conversion to methadone is not as straight forward as indicated above and would need close monitoring of titration. TD: Transdermal, IV: Intravenous

important to understand that pain in cancer should never be treated in isolation from cancer *per se* and recognize the side effects of treatments and cancer itself. Education and feedback from the patient and relatives are important in the prescribing of opioids as well as adjusting the dose for each individual.

Constipation

Constipation must be expected when treatment with opioids for pain relief is initiated. Among patient with advanced cancer, the reported prevalence[31] of constipation is between 40% and 90%, especially in population on an opioid prescription.[32,33] Increasing age, reduced mobility, reduced hydration, polypharmacy, structural issues, pain, and metabolic aberration are further contributing factors.[34,35] Recommendation in palliative and advanced cancer population is derived from extrapolation from studies on constipation arising from nonmalignancy condition.[36-38] Assessment through detailed history is essential in preventing chronic constipation. The Rome IV Criteria for functional gastrointestinal disorders have included opioid-induced constipation (OIC) under the section on "Bowel Disorders," defined as "constipation triggered or worsened by opioid analgesics."[39]

Naloxegol, naldemedine methyl naltrexone, is the peripherally acting μ-opioid receptor antagonists; a newer class of agents addressing the peripheral effect of opioids has been approved for OIC. Combined opioid/naloxone has been shown to reduce the risk of OIC through phase II and phase III studies but are currently not available in India.[40-42] If intractable chronic constipation, opioid rotation to fentanyl or methadone should be considered, though these drugs can also cause constipation.

While relief of constipation through pharmacological methods is attempted, nonpharmacological methods including reference to onco-nutritionist and changes in daily routines and habits play a vital role in its management.[43]

There is a consensus that laxative treatment should commence with the opioid therapy and continue throughout treatment. A combination of high-fiber diet, increase water intake, a bed-time laxative (Stimulant) with a stool softener, and assurance of patient through appropriate communication gives better results. Even when other laxatives are prescribed, approximately half of patients treated for OIC do not achieve the desired improvement.[43] Moreover, laxatives do not target the underlying cause of OIC-opioid binding to the μ receptors in the enteric system and as such are not very effective at managing OIC.

Nausea and vomiting

The etiology of nausea and vomiting in advanced disease can be multifaceted and includes cerebral causes, metastatic causes, biochemical syndromes, infections, vestibular causes, paraneoplastic causes, dyspepsia or gastritis, anxiety, opioid induced, constipation, or malignant bowel obstruction.

There is no randomized controlled trial evaluating the efficacy of antiemetics such as haloperidol,[44] levomepromazine,[45] and olanzapine[46,47] for the treatment of nausea and vomiting in palliative care patients. Evidence is based on systematic review and case studies. Olanzapine was studied in a case series and found to be of use in difficult to control nausea and vomiting. Recommendations could not be made on low-to-moderate-quality randomized clinical trial (around 9 in number) evaluating metoclopramide and dexamethasone.

Opioid-induced nausea and vomiting has varied pathology. The choice of antiemetic would hence need to be directed by the pathophysiology. The patient develops tolerance to this side effect commonly, 5–10 days after starting treatment.

In malignant bowel obstruction, octreotide has been studied, along with glucocorticoids, antipsychotics, antiemetics, and anticholinergics. It has been reported to have improvement in nausea and vomiting when started at time of diagnosis,[48-50] decrease nasogastric tube drainage output,[51] and provide good symptom control.

Pruritis

Pruritus (itch) is an occasional side effect of opioid use and is more commonly seen with epidural or intrathecal routes of morphine administration.[52] This could indicate that the spinal opioid receptors could be involved.[53] Histamine release from mast cells has been reported with the administration of opioids, mainly morphine.[54] Opioids may enhance itch by disinhibition of recently described itch-specific neuron. Treatment of this side effect hence depends on the postulated cause.

Antihistamines such as diphenhydramine and cetirizine can be used. The sedating effect of diphenhydramine may be an advantage in relieving the itch. Serotonin antagonist ondansetron has been studied and found to be helpful. A μ-opioid receptor antagonist such as naloxone can be used, titrated gradually for relief of the symptom. However, the possibility of reversal of analgesia should be considered. If the pruritus persists, despite adequate symptomatic management, then consideration of switching opioids should be entertained.[55]

No randomized studies are present in literature for this side effect management.

Delirium

Mild cognitive impairment is unlikely to be caused by an opioid after 2 weeks of steady-stable dosage. Delirium, an acute confusional state, is characterized with mental clouding, leading to disturbances in consciousness and comprehension of events. The presence of various causes of delirium that occur in those who are terminally ill makes a diagnosis of opioid-induced delirium complicated. It could be considered as part of the differential diagnosis. In addition, patients are at greater risk of opioid-induced delirium if they have hepatic/renal dysfunction. They already have a degree of cognitive impairment, are dehydrated, or are taking other psychoactive drugs.[52]

A Cochrane review found that four opioids had less than 5% impact on delirium and hallucination.[56]

Sedation

Incidence of sedation has been reported to be between 20% and 60% during the initiation of opioid therapy or with increased dose titration.[57] It is essential to understand the difference between cancer-induced fatigue and opioid-induced sedation. Interactions with other medications should be considered. Reduction in the dosage of the opioid and addition of adjuvants to reduce the opioid dose can be considered.[58]

There is limited evidence for the routine use of psychostimulants.[59]

Patients who have an altered sleep-wake cycle and those who have poor pain control affecting sleep will need education and adjustment of analgesics for pain relief. This could lead to "catch-up sleep" which could last a couple of days and should be explained to relatives.[55]

Nonpharmacological methods to maintain a normal sleep-wake cycle should be encouraged, along with good sleep hygiene.

Respiratory depression

Respiratory depression is a clinical concern among patients receiving opioids. This unfortunately could mean that pain i s often under-treated and hence leads to poor-quality pain management in patients. When opioids are taken orally, with gradual titration, the risk of this complication is minimal. Should respiratory depression occur in such cases, an alternate cause causing respiratory or cardiac decompensation should be considered, including polypharmacy with drug interactions.[60]

Increased somnolence and/or sedation are the first symptoms preceding respiratory depression. When rapidly titrating or escalating the dosage, careful monitoring of the level of consciousness is a better indicator for the early recognition of respiratory depression.[61]

If respiratory depression is suspected, then μ-opioid receptor antagonists such as naloxone should be titrated, cautiously monitoring for recurrence of pain, which should be managed using another group of pain medication until the patient is stabilized.

Naloxone 1 ampoule (1 ml = 0.4 mg/40 mcg) is made up to 10 ml with addition of 9 ml normal saline (each ml is now equal to 0.04 mg). 1–2 ml (0.04–0.08 mg) is given every 60 s until reversal of symptoms. With the half-life of naloxone being 30–80 min, careful monitoring should be continued, with the understanding that the dose may need to be repeated. If there is no improvement noted after a total of 1 mg of naloxone, then another reason for the respiratory depression should be sought. Reversal of respiratory depression from buprenorphine requires a higher dose of naloxone.[55,62]

Conclusion

The ISSP Cancer Pain SIG guidelines on pharmacological management of cancer pain in adults emphasizes that oral morphine should be started in low doses and every 4 hourly. Here, we also emphasize the use of transdermal fentanyl as an opioid of choice for opioid rotation. We also emphasize that laxatives should always be prescribed along with strong opioids and naloxone should be used for opioid-induced respiratory depression [Table 2].

Table 2: Summary of recommendations

Recommendations	Level of evidence
Morphine should be started at the dose of 5-10 mg 4-hourly using the oral IR formulation (Grade B)	IIb
In the elderly and frail, a lower starting dose of 2.5-5 mg 4-6-hourly of the IR formulation should be used (Grade B)	IIb
Double dose at bedtime is recommended (GCP)	V
IV morphine for rapid titration for severe pain (Grade A)	Ib
Chronic cancer pain patients should receive regular ATC opioid therapy (Grade B)	IIb
SR formulation can be started 12 hourly, once the effective 24 h dose is established (GCP)	V
The ratio of the BTcP rescue medication should be 1/12 to 1/6 of the total 24 h dose (GCP)	V
OTFC should be the choice of BTcP medication (Grade A)	Ia
Opioid switch or rotation should be considered if there is inadequate analgesia or intolerable side effects (Grade B)	IIa
Transdermal fentanyl is the opioid of choice for opioid conversion (Grade D)	V
Different mode of administration should be considered for patients who cannot tolerate oral ingestion (Grade B)	IIa
Methadone equianalgesic dose rotation should be carried out under clinical supervision in experienced hands (Grade B)	IIa
All cancer patients should be evaluated for constipation (Grade D)	V
If constipation is identified, physical examination should include abdominal examination, perineal inspection and DRE (GCP)	V
Laxatives must be routinely prescribed for both the prophylaxis and the management of opioid induced constipation (Grade B)	IIa
Metoclopramide should be recommended for treatment of opioid-related nausea/vomiting (Grade B)	IIb
Opioid rotation and route switching may be effective approaches in refractory cases (Grade B)	IIb
For opioid-induced respiratory depression, μ receptor antagonists (e.g. naloxone) must be used promptly (Grade A)	Ib

IR: Immediate release, ATC: Around the clock, SR: Sustained-release, IV: Intravenous, BTcP: Breakthrough cancer pain, OTFC: Oral transmucosal fentanyl citrate, GCP: Good clinical practice, DRE: Digital rectal examination

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.

Acknowledgments

The ISSP Cancer Pain SIG guidelines' GDC would like to thank the President, Secretary of ISSP, the Governing Council of ISSP, as well as the Chairman of SIG. The ISSP Cancer Pain SIG guidelines' GDC would like to thank the members of the ISSP, the IAPC, and other anaesthesiologists who responded

to the questionnaire and gave their valuable feedback which helped in the formulation of these guidelines.

The ISSP Cancer Pain SIG would like to wholeheartedly thank the internal review committee and the external review committee.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mercadante S, Porzio G, Ferrera P, Fulfaro F, Aielli F, Ficorella C, *et al*. Low morphine doses in opioid-naive cancer patients with pain. J Pain Symptom Manage 2006;31:242-7.
2. De Conno F, Ripamonti C, Fagnoni E, Brunelli C, Luzzani M, Maltoni M, *et al*. The MERITO Study: A multicentre trial of the analgesic effect and tolerability of normal-release oral morphine during 'titration phase' in patients with cancer pain. Palliat Med 2008;22:214-21.
3. Dale O, Piribauer M, Kaasa S, Moksnes K, Knobel H, Klepstad P. A double-blind, randomized, crossover comparison between single-dose and double-dose immediate-release oral morphine at bedtime in cancer patients. J Pain Symptom Manage 2009;37:68-76.
4. Harris JT, Suresh Kumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. Palliat Med 2003;17:248-56.
5. Casamayor M, DiDonato K, Hennebert M, Brazzi L, Prosen G. Administration of intravenous morphine for acute pain in the emergency department inflicts an economic burden in Europe. Drugs Context 2018;7:212524.
6. 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.
7. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. Cochrane Database Syst Rev 2016;4:CD003868.
8. Davies AN, Elsner F, Filbet MJ, Porta-Sales J, Ripamonti C, Santini D, *et al*. Breakthrough cancer pain (BTcP) management: A review of international and national guidelines. BMJ Support Palliat Care 2018;8:241-9.
9. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA 1984;252:1905-7.
10. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the Opioid Risk Tool. Pain Med 2005;6:432-42.
11. Belgrade MJ, Schamber CD, Lindgren BR. The DIRE score: Predicting outcomes of opioid prescribing for chronic pain. J Pain 2006;7:671-81.
12. Skinner HA. The drug abuse screening test. Addict Behav 1982;7:363-71.
13. Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). J Pain 2008;9:360-72.
14. Schneider JP. Opioids pain management and addiction. Pain Pract Winter 2006;16:17-24.
15. Gazette Notification G.S.R. 359(E) dated 5th May 2015 Issued Amending the Narcotic Drugs and Psychotropic Substances Rules, 1985, Namely Called the Narcotic Drugs and Psychotropic Substances (Third Amendment) Rules; 2015.
16. Passik SD, Weinreb HJ. Managing chronic nonmalignant pain: Overcoming obstacles to the use of opioids. Adv Ther 2000;17:70-83.
17. Deandrea S, Corli O, Consonni D, Villani W, Greco MT, Apolone G. Prevalence of breakthrough cancer pain: A systematic review and a pooled analysis of published literature. J Pain Symptom Manage 2014;47:57-76.
18. Sperlinga R, Campagna S, Berruti A, Laciura P, Ginosa I, Paoletti S, *et al*. Alberta Breakthrough Pain Assessment Tool: A validation multicentre study in cancer patients with breakthrough pain. Eur J Pain 2015;19:881-8.
19. Zeppetella G. Opioids for the management of breakthrough cancer pain in adults: A systematic review undertaken as part of an EPCRC opioid guidelines project. Palliat Med 2011;25:516-24.
20. Zeppetella G, Riberio MD. Opioids for the management of breakthrough episodic pain in cancer patients. Cochrane Database Syst Rev 2006;1:CDOO4311.
21. Jandhyala R, Fullarton JR, Bennett MI. Efficacy of rapid-onset oral fentanyl formulations vs. oral morphine for cancer-related breakthrough pain: A meta-analysis of comparative trials. J Pain Symptom Manage 2013;46:573-80.
22. Nalamachu SR. Opioid rotation in clinical practice. Adv Ther 2012;29:849-63.
23. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: The science and the limitations of the equianalgesic dose table. J Pain Symptom Manage 2009;38:426-39.
24. Schuster M, Bayer O, Heid F, Laufenberg-Feldmann R. Opioid rotation in cancer pain treatment. Dtsch Arztebl Int 2018;115:135-42.
25. Scottish Intercollegiate Guidelines Network. Control of Pain in Adults with Cancer. Edinburgh: Scottish Intercollegiate Guidelines Network; 2008.
26. Tassinari D, Sartori S, Tamburini E, Scarpi E, Raffaeli W, Tombesi P, *et al*. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: A meta-analysis and systematic review of the literature. J Palliat Med 2008;11:492-501.
27. Radbruch L, Trottenberg P, Elsner F, Kaasa S, Caraceni A. Systematic review of the role of alternative application routes for opioid treatment for moderate to severe cancer pain: An EPCRC opioid guidelines project. Palliat Med 2011;25:578-96.
28. 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.
29. Shaheen PE, Walsh D, Lasheen W, Davis MP, Lagman RL. Opioid equianalgesic tables: Are they all equally dangerous? J Pain Symptom Manage 2009;38:409-17.
30. Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. J Clin Oncol 2003;21:87s-91s.
31. Larkin PJ, Sykes NP, Centeno C, Ellershaw JE, Elsner F, Eugene B, *et al*. The management of constipation in palliative care: Clinical practice recommendations. Palliat Med 2008;22:796-807.
32. Thorpe DM. Management of opioid-induced constipation. Curr Pain Headache Rep 2001;5:237-40.
33. Goodman M, Low J, Wilkinson S. Constipation management in palliative care: A survey of practices in the United Kingdom. J Pain Symptom Manage 2005;29:238-44.
34. Bouras EP, Tangalos EG. Chronic constipation in the elderly. Gastroenterol Clin North Am 2009;38:463-80.
35. Van Lancker A, Velghe A, Van Hecke A, Verbrugghe M, Van Den Noortgate N, Grypdonck M, *et al*. Prevalence of symptoms in older cancer patients receiving palliative care: A systematic review and meta-analysis. J Pain Symptom Manage 2014;47:90-104.
36. Dukas L, Willett WC, Giovannucci EL. Association between physical activity, fiber intake, and other lifestyle variables and constipation in a study of women. Am J Gastroenterol 2003;98:1790-6.
37. Winge K, Rasmussen D, Werdelin LM. Constipation in neurological diseases. J Neurol Neurosurg Psychiatry 2003;74:13-9.

38. Boland JW, Boland EG. Pharmacological therapies for opioid induced constipation in adults with cancer. BMJ 2017;358:j3313.
39. Tack J, Drossman DA. What's new in Rome IV? J Neurogastroenterol Motil 2017;29:E13053.
40. Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. Cochrane Database Syst Rev 2011;1:CD003448.
41. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med 2014;370:2387-96.
42. Katakami N, Harada T, Murata T, Shinozaki K, Tsutsumi M, Yokota T, *et al*. Randomized phase III and extension studies of naldemedine in patients with opioid-induced constipation and cancer. J Clin Oncol 2017;35:3859-66.
43. Sizar O, Gupta M. Opioid induced constipation. In: Stat Pearls. Treasure Island (FL): Stat Pearls Publishing; 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493184. [Last updated on 2019 Jun 04].
44. Storrar J, Hitchens M, Platt T, Dorman S. Droperidol for treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev 2014;11:CD006938.
45. Cox L, Darvill E, Dorman S. Levomepromazine for nausea and vomiting in palliative care. Cochrane Database Syst Rev 2015;11:CD009420.
46. MacKintosh D. Olanzapine in the management of difficult to control nausea and vomiting in a palliative care population: A case series. J Palliat Med 2016;19:87-90.
47. Atkinson SR. Olanzapine for intractable nausea and vomiting in palliative care patients not receiving chemotherapy. J Palliat Med 2014;17:503-4.
48. Watari H, Hosaka M, Wakui Y, Nomura E, Hareyama H, Tanuma F, *et al*. A prospective study on the efficacy of octreotide in the management of malignant bowel obstruction in gynecologic cancer. Int J Gynecol Cancer 2012;22:692-6.
49. Kubota H, Taguchi K, Kobayashi D, Naruyama H, Hirose M, Fukuta K, *et al*. Clinical impact of palliative treatment using octreotide for inoperable malignant bowel obstruction caused by advanced urological cancer. Asian Pac J Cancer Prev 2013;14:7107-10.
50. Peng X, Wang P, Li S, Zhang G, Hu S. Randomized clinical trial comparing octreotide and scopolamine butylbromide in symptom control of patients with inoperable bowel obstruction due to advanced ovarian cancer. World J Surg Oncol 2015;13:50.
51. Hisanaga T, Shinjo T, Morita T, Nakajima N, Ikenaga M, Tanimizu M, *et al*. Multicenter prospective study on efficacy and safety of octreotide for inoperable malignant bowel obstruction. Jpn J Clin Oncol 2010;40:739-45.
52. McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, *et al*. Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. J Pain 2003;4:231-56.
53. Szarvas S, Harmon D, Murphy D. Neuraxial opioid-induced pruritus: A review. J Clin Anesth 2003;15:234-9.
54. Withington DE, Patrick JA, Reynolds F. Histamine release by morphine and diamorphine in man. Anaesthesia 1993;48:26-9.
55. Swarm R, Abernethy AP, Anghelescu DL, Benedetti C, Blinderman CD, Boston B, *et al*. Adult cancer pain. J Natl Compr Canc Netw 2010;8:1046-86.
56. Wiffen PJ, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. Cochrane Database Syst Rev 2014;5:CD011056.
57. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, *et al*. Strategies to manage the adverse effects of oral morphine: An evidence-based report. J Clin Oncol 2001;19:2542-54.
58. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Fam Physician 2006;74:1347-54.
59. Wilwerding MB, Loprinzi CL, Mailliard JA, O'Fallon JR, Miser AW, van Haelst C, *et al*. A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. Support Care Cancer 1995;3:135-8.
60. Lyss AP, Portenoy RK. Strategies for limiting the side effects of cancer pain therapy. Semin Oncol 1997;24:S16-28-34.
61. Jungquist CR, Smith K, Nicely KL, Polomano RC. Monitoring hospitalized adult patients for opioid-induced sedation and respiratory depression. Am J Nurs 2017;117:S27-S35.
62. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. Anesthesiology 2010;112:226-38.

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?

Appendix VI

Name of Institution ……

Name of Patient……. Reg No……. Unit……

Age/Sex……. Diagnosis…….

Opioid Consent Form

Opioid analgesics are medications used to treat moderate to severe pain. The aim of treatment is to relieve pain with all the efforts to minimize drug related side effects and to improve Quality of life of patient. The Pain and Palliative Care team will monitor the effects of pain and treat that pain appropriately.

I, _____, understand that I need to follow the guidelines below to receive pain treatment with opioids by the pain/palliative care physician of the institute.

- I will take medications only at the dose and frequency prescribed.
- I will take no additional opioid analgesics unless talked to the pain/palliative care physician.
- No increase in pain medication will be made without prior approval from pain/palliative care physician.
- I will keep my scheduled appointments. If I need to cancel an appointment, I will give 24 hours prior notice.
- I will not use illegal drugs or substance during treatment.
- I will consent to random drug screens if indicated or requested by pain/palliative care physician.
- I understand that opioid analgesic pain medications may be stopped if any one of the following events occurs:
  - The care provider feels that opioid analgesics are not helping to relieve my pain or my ability to function as not improved.
  - I repeatedly fail to follow care providers' instructions on the use of opioids.
  - I develop side effects that are of concern to the care providers.
  - Inappropriately obtain opioids from source other than this institute.
- I or my relative will come to refill the prescription of medication 48 to 96 hours prior to needing them.
- If pain/palliative care physician chooses to stop opioid analgesic medication, either it will be reduced over a safe period of time or a referral will be made to an alternate care provider.
- An important part of pain management may include non-drug therapies. If I do not follow through with all of the parts of this plan, I understand that the need for opioid therapy may be re-evaluated.
- I will protect my prescription and medication. If medication or prescription are stolen, it must be reported to police and case number will be given to healthcare provider of this institute. Treatment with opioid analgesics will be re-evaluated and may include discontinuation of care for recurrent losses.

- When appropriate, I consent to allow pain/palliative care physician to share information with other providers of my medical care.

Patient's Sign _____ Date: _____

Caregiver's Sign _____ Date: _____

Doctor's Sign _____ Date: _____

Appendix VII (Courtesy: Dr. Raghu S Thota, Professor, Tata Memorial Centre (Homi Bhabha National Institute), for Appendix VII)

Pain Control in Emergency (Rapid IV MORPHINE Titration):

Why: To reduce the pain severity of patient presenting to Emergency Department

Who: The CMO or respective oncological services (The patient should be under direct medical supervision)

Where: In the emergency department

What: IV morphine to control severe pain

When: Any adult patients, presenting to ED with severe pain

How: (please do the following)

- Assess for Pain (NRS, 0-10 scale)
- Severe Pain ≥7
- Rule out Red flags
- Secure IV cannula
- Monitor SpO_2, Pulse, RR, BP (Pain 5th Vital sign).
- Connect O_2 by mask
- Calculate and load IV Morphine dose (0.1mg/kg) and dilute in 10ml using NS and to be injected IV over 5 minutes

Cancer pain emergencies and or Red flags

1. Bone fracture or impending fracture of weight bearing bone
2. Epidural metastases
3. Leptomeningeal metastases
4. Infection
5. Obstructed or perforated viscus (acute abdomen)
6. Recurrence of the disease

Opioid naïve includes patients who are not chronically receiving opioid analgesics on a daily basis and therefore have not developed significant tolerance.

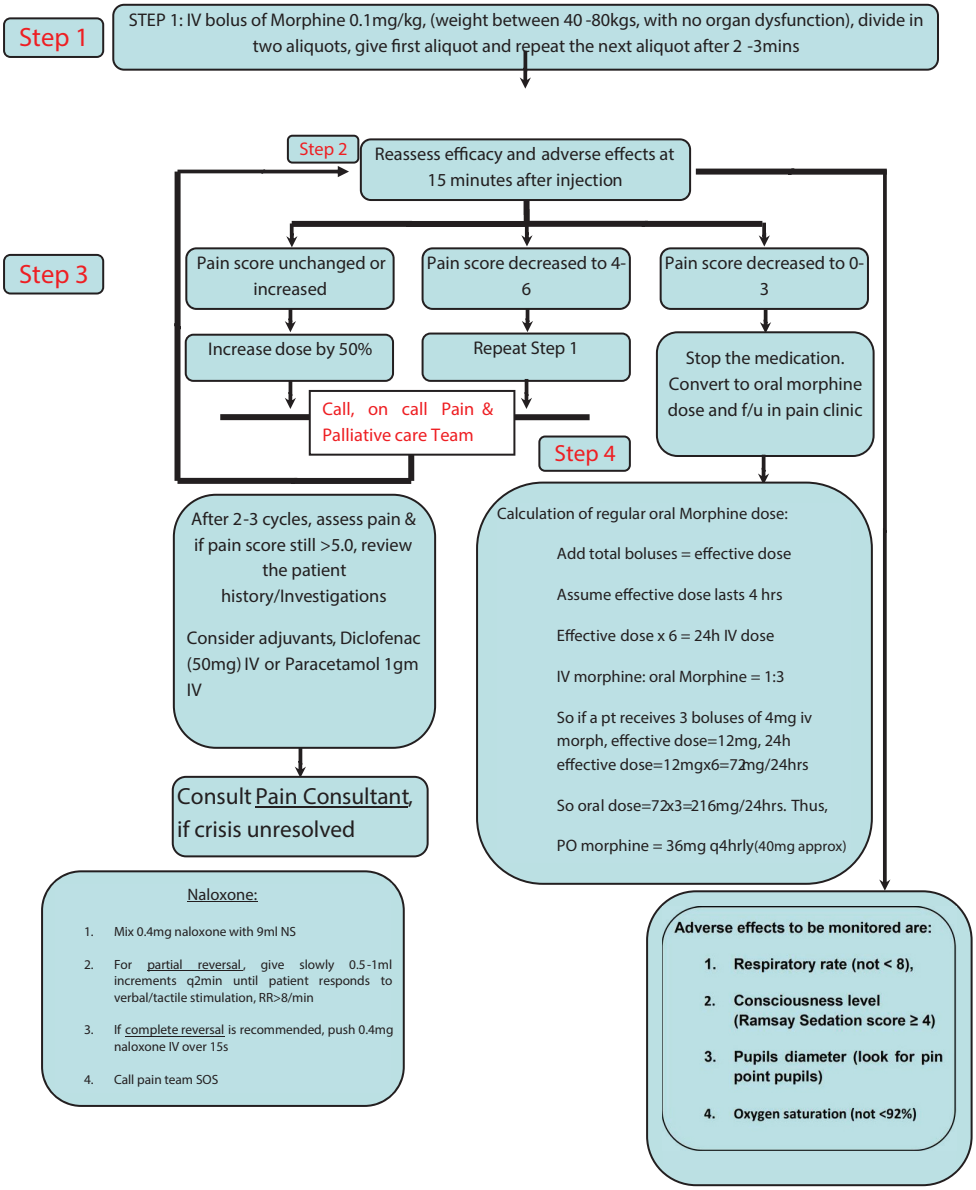
Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as patients receiving at least 60mg of morphine daily or an equianalgesic dose of another opioid for a week or longer.

Opioid tolerant patient:

Everything is similar as of Opioid Naïve patient, except for the **Step one**:

Step1: Intravenous bolus of IV Morphine 10-20% of the total opioid (Morphine or equivalent) taken in the previous 24 hours

Opioid Naïve Patients:



References

1. Hagen NA, Elwood T, Ernst S. Cancer pain emergencies: A protocol for management. J Pain Symptom Manage 1997;14:45-50.
2. NCCN Clinical Practice Guidelines in Oncology. Adult Cancer Pain, Version 2; 2013.
3. Mercadante S, Villari P, Ferrera P, Casuccio A, Fulfaro F. Rapid titration with intravenous morphine for severe cancer pain and immediate oral conversion. Cancer 2002;95:203-8.