

Pain Management for Cancer Patient`S Using Painkiller`S

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ABSTRACT

The WHO analgesic ladder outlines a three-step strategy for managing cancer pain, tailoring analgesic interventions based on the severity of pain in a universally applicable manner. For mild pain, nonopioids are recommended, with the inclusion of mild opioids for moderate pain and potent opioids for severe pain. In this context, we examine the supporting evidence for the utilization of painkillers in cancer patients.

Scientific evidence endorses the use of anti-inflammatory drugs like acetaminophen/paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) for addressing mild cancer pain. Combining an NSAID with an opioid proves effective for more intense pain; however, the potential long-term adverse effects remain unquantified. Limited evidence exists to advocate for the combination of acetaminophen with potent opioids. Corticosteroids play a specific role in cases of spinal cord compression and brain metastases, where enhanced analgesia is a secondary advantage. The evidence is less conclusive for incorporating corticosteroids alongside potent opioids when pain management is the primary goal.

Systematic reviews suggest the potential utility of antidepressants and anticonvulsant medications in treating neuropathic pain, but methodological concerns persist in the available studies. In certain tumor types, bisphosphonates demonstrate efficacy in alleviating pain associated with bony metastases. Denosumab, compared to bisphosphonates, may delay the progression of pain worsening.

KEY WORDS: NSAIDS, Nonopioids , Analgesic Ladder Outlines, Acetaminophen, Mild Opioids /Potent Opioids .

I. INTRODUCTION

General Information About Cancer Pain

Certainly, understanding and effectively managing cancer pain is crucial for improving patients' quality of life.

Effective pain management typically involves assessing the severity and cause of the pain, considering both pharmacological and non-pharmacological interventions, and adjusting the treatment plan based on individual responses and needs. Regular communication between healthcare providers and patients is essential for optimal outcomes.[1]

1.Regular screening is crucial to promptly identify and address the patient's pain. Timely recognition allows healthcare providers to tailor interventions and ensure more effective pain management. For additional details, refer to the Pain Assessment section for comprehensive information on evaluating and understanding the patient's pain experience.

2.Accurate characterization of pain aids in uncovering its underlying causes, shaping a more informed approach to treatment. Explore the Pain Classification section for detailed insights into categorizing pain based on its nature, helping guide appropriate and targeted interventions.

- Is the pain acute or chronic ?
- Is it secondary to cancer, cancer treatment, other causes, or a combination?
- Is it somatic, visceral, neuropathic, or mixed?
- Is there an incidental component?
- Is there breakthrough pain?

3. The importance of considering various factors when determining the appropriate treatment for pain, including psychological distress and substance use.For more information, see the **Background and Definitions** section

- What is the impact of pain on the patient?
- Is the benefit of treatment likely going to outweigh the risks?

4. Identifying the optimal treatment for pain involves considering both pharmacological and nonpharmacological options. It's essential to explore a range of approaches and, when necessary, make referrals to specialists who can provide targeted expertise.

There are many issues to consider when determining the most appropriate treatment, such as the following:

- a. Previous pain treatments.
- b. Patient prognosis.
- c. Predictive factors for pain control (e.g., psychological distress).
- d. Impact on function.
- e. Comorbidities (e.g., renal or hepatic failure).
- f. Risk of misuse of or addiction to pain medications.
- g. Patient preference.

5. Proper education about treatment is crucial, encompassing details such as medication administration, expected side effects, associated treatments, and realistic expectations for improvement. If opioids are part of the plan, addressing concerns and educating patients and caregivers about the risks, safe usage, storage, and disposal is essential. It's noteworthy that improper use, storage, and disposal have been observed, emphasizing the importance of thorough education, especially in cancer outpatient settings.[2]

6. Monitoring patients longitudinally with regular visits is a crucial aspect of pain management, allowing for the adjustment of treatments as needed. Close monitoring is particularly important for patients with chronic pain, whether due to cancer or other causes, to optimize treatment and minimize the risk of complications associated with opioid use. Regular evaluations of the risks and benefits of opioid use, along with open discussions between physicians and patients, contribute to a comprehensive and patient-centered approach to pain management.

Background and Definitions

The definition from the International Association for the Study of Pain encapsulates pain as not only an unpleasant sensory experience but also one with emotional components. It emphasizes the connection between pain and actual or potential tissue damage.[3]

Pain is commonly experienced by cancer patients. Its proper assessment requires the following:

- a. Measuring pain involves assessing various factors, including location(s), intensity, and quality, along with other relevant factors. This comprehensive evaluation helps healthcare professionals gain a detailed understanding of the pain experience, facilitating more effective treatment strategies.
- b. Clarifying the impact of pain on patients' psychological, social, spiritual, and existential

domains is essential for a holistic understanding of their experience. It allows healthcare professionals to address not only the physical aspect of pain but also its broader implications, contributing to a more comprehensive and patient-centered approach to care.

- c. Establishing treatment adherence and responsiveness is crucial in pain management. This involves ensuring that patients follow their treatment plans and assessing how well the chosen interventions are working for them. Regular communication between healthcare providers and patients helps tailor treatments for optimal effectiveness.

Certainly, pain intensity assessment commonly involves using a Numeric Rating Scale (NRS), where patients rate their pain on a scale of 0 to 10. This scale helps quantify the subjective experience of pain, with 0 representing no pain and 10 indicating the worst pain imaginable. It provides a straightforward way for patients to communicate the intensity of their pain.[4]

The three-step World Health Organization (WHO) pain relief ladder is indeed a commonly used approach in pain management. It categorizes pain intensity based on severity and recommends analgesic agents at different steps, starting with non-opioid medications and progressing to opioids as needed. This framework provides a structured guide for tailoring pain management strategies to the level of pain intensity.[5]

Indeed, familiarity with opioid pharmacokinetics, equianalgesic dosing, and potential adverse effects is crucial for the safe and effective use of opioids in pain management. Additionally, incorporating adjuvant pharmacological and nonpharmacological interventions is essential to optimize pain management strategies. This comprehensive approach allows for a more tailored and balanced approach to addressing pain.

The prevalence of pain in patients with cancer is significant, ranging from 20% to 50%. In advanced-stage cancer, approximately 80% of patients experience moderate to severe pain. A meta-analysis of 52 studies revealed that more than half of cancer patients report pain. Notably, younger patients are more likely to experience both cancer pain and pain flares compared to older patients.

CAUSES OF CANCER PAIN

In a study of 100 patients with advanced cancer seeking palliative care, the primary tumor was identified as the chief cause of pain in 68% of cases.[10] Additionally, the study observed that most pain was somatic, and there was an equal likelihood of pain being continuous as opposed to intermittent.

Pain can be caused by following ;

- a. Surgery
- b. Radiation therapy
- c. Chemotherapy
- d. Targeted therapy
- e. Supportive care therapy
- f. Diagnostic procedure

According to a systematic review, pain is reported in 59% of patients undergoing anticancer treatment and in 33% of patients after curative treatments. However, the prevalence of chronic nonmalignant pain, including conditions like chronic low back pain, osteoarthritis pain, fibromyalgia, and chronic daily headaches, has not been well characterized in cancer patients. Reported prevalence ranges from 2% to 76%, varying based on the patient population and assessment methods.[11-14]

Chemotherapy-related musculoskeletal pain

Paclitaxel is known to induce a syndrome of diffuse arthralgias and myalgias in 10% to 20% of patients.[33] This pain, affecting joints and muscles, typically emerges 1 to 2 days post-infusion and lasts around 4 to 5 days. It originates in areas such as the back, hips, shoulders, thighs, legs, and feet, with exacerbation upon weight bearing, walking, or tactile contact. Steroids may help mitigate the development of myalgia and arthralgias in such cases. Aromatase inhibitors among hormonal therapies can also cause musculoskeletal symptoms, osteoporotic fractures, arthralgias, and myalgias.[34]

Supportive care therapies and pain

Supportive care therapies can contribute to pain, exemplified by bisphosphonate-associated osteonecrosis of the jaw.[41] Additionally, the use of corticosteroids has been linked to the development of avascular necrosis, highlighting the need for careful consideration of potential side effects and complications in the context of supportive care.[42]

Radiation-induced pain

Radiation therapy can indeed induce various pain syndromes, including discomfort from

brachytherapy and positioning during treatment. Delayed tissue damage, such as mucositis and dermatitis, may contribute to pain. Additionally, a notable side effect is the temporary worsening of pain, termed a pain flare, which can occur with radiation treatment for bone metastases.[43] Notably, a randomized trial demonstrated that dexamethasone, when administered during and after radiation therapy, reduces the incidence of such pain flares compared with a placebo.[44]

What cancer causes the most pain?[93-97]

The subjective nature of pain makes it challenging to quantify. The analysis revealing the significant pain impact of pancreatic cancer, with 72% of individuals reporting cancer pain, underscores the complex and individualized nature of pain experiences. The high prevalence of cancer pain in advanced stages further emphasizes the importance of personalized and comprehensive pain management in oncology.

Impact on Function and QOL[45,46]

Cancer pain is indeed linked to heightened emotional distress, and the risk of developing depression correlates with both the duration and severity of pain. The impact on daily life is significant, with cancer patients being disabled for an average of 12 to 20 days per month, and a considerable percentage unable to work due to their condition.[45] Furthermore, cancer survivors may face emotional distress when pain persists post-treatment, and the transition of care from oncologists to primary care providers can result in a loss of support.

In a study, it was observed that between 20% and 50% of cancer patients continued to experience pain and functional limitations even years after treatment.[47] Notably, untreated pain can have serious consequences, including an increased likelihood of requests for physician-assisted suicide.[48] Additionally, untreated pain contributes to unnecessary hospital admissions and visits to emergency departments.[49] Addressing and managing pain effectively are crucial aspects of comprehensive cancer care.

PHARMACOLOGICAL THERAPIES FOR PAIN CONTROL

- A. Non-opioid pain medication [93-97]-** These medications include: Acetaminophen
- B. Nonsteroidal Anti-inflammatory(NSAIDs)-** such as ibuprofen

C. Opioid pain medication- Opioids may include:

- a) Hydrocodone
- b) Hydromorphone
- c) Oxycodone
- d) Methadone
- e) Fentanyl skin patch
- f) Buprenorphine transdermal patch
- g) Buprenorphine buccal lm
- h) Buprenorphine
- i) Morphine

ACETAMINOPHEN AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Acetaminophen and NSAIDs are often initiated for mild pain and prove useful as adjunct agents to opioids in managing moderate to severe pain. No single NSAID is preferred over others, and all demonstrate better analgesic efficacy than placebo.[51] As opioid adjuncts, acetaminophen and NSAIDs have shown benefits in improving analgesia and reducing opioid use. However, caution is advised, and they may be avoided in older patients or those with renal, hepatic, or cardiac disease.[51] For more details, you can refer to the section on Geriatric cancer patients in the

"Treatment of Pain in Specific Patient Populations."

Indeed, while acetaminophen and NSAIDs can provide analgesia independently, several randomized controlled trials have reported that adding either agent to opioids may enhance pain control and reduce the need for opioids in cancer patients.[52-54] It's worth noting that the extent of these benefits varied across trials and was not consistently observed. The individualized nature of patient response underscores the importance of a tailored approach to pain management. [55-56]

High-potency NSAIDs like ketorolac and diclofenac have been extensively studied and shown benefits in managing cancer pain. However, there is no conclusive comparative data establishing the superiority of one product over another among these agents. Gastrointestinal irritation, ulcer formation, and dyspepsia are common side effects, with additional concerns including cardiotoxicity, nephrotoxicity, hepatotoxicity, and hematologic effects.[57-58] Cyclooxygenase-2 (COX-2)-specific agents, such as celecoxib, may offer a more favorable gastrointestinal side effect profile but at a higher cost.[57] Nonetheless, long-term safety and efficacy data for these agents remain unclear.

Table 1. Acetaminophen and Selected Nonsteroidal Anti-inflammatory Analgesics

Drug	Dosage	Comments	Reference(s)
Acetaminophen	<4,000 mg/d	Dosed every 4 to 8 hours, depending on dose and product used.	[52]
Celecoxib	200–400 mg/d	COX-2 specific. Minimal antiplatelet effects compared with nonselective NSAIDs.	[57]
Diclofenac	100–200 mg/d	Available as immediate- and delayed/extended-release products.	[59]
Ibuprofen	600–2,400 mg/d		[59]
Ketoprofen	100–300 mg/d	Available as parenteral in some parts of the world, which may be preferred.	[57 ,60]
Ketorolac	40–60 mg/d, generally dosed every 6 hours	Parenteral (IV, IM) ketorolac is used ≤5 days because of concerns about GI adverse events. May also be given PO.	[57]

Abbreviations ;COX-2 = cyclooxygenase-2; GI = gastrointestinal; IM = intramuscular; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = by mouth

Table 2. Selected Opioid Analgesics

Opioid Drug	Equianalgesic Dosing	Comments	Reference(s)
Buprenorphine	No consensus.	Available in transdermal and sublingual forms. May induce fewer instances of constipation and nausea compared to other opioids..	[66 - 68]
Codeine	Oral: 200 mg	Maximum of 360 mg/d. Used with or without acetaminophen.	[51 ,69]
Fentanyl	Transdermal: 12 µg/h × 24 h ~ 25 mg oral morphine/day. Transmucosal: no consensus; varies by product.	Administered through transdermal, transmucosal, or intravenous routes. Patients with cachexia may experience reduced absorption from transdermal patches.	[69 - 71]
Hydrocodone	Immediate release formulation with acetaminophen: 20 mg	Equianalgesic dose calculations for extended-release products vary; see prescribing information.	[51 ,72]
Hydromorphone	Oral: 6-7.5 mg, IV: 1.5 mg		[60 ,73]
Methadone	Equianalgesic ratio varies widely by dose.	Used primarily for severe pain in non-opioid-naïve patients. Unusual pharmacokinetics require experienced practitioner.	[51 ,74 ,75]
Morphine	Oral: 30 mg, IV: 10 mg	Randomized trials supporting use. First-choice opioid because of familiarity, availability, and cost.	[51 ,69]
Opioid Drug	Equianalgesic Dosing	Comments	Reference(s)
Oxycodone	20 mg	Randomized trials supporting use.	[69]
Oxymorphone	10 mg		[60]
Tapentadol	100 mg	Similar to morphine, 30-40 mg.	[73,76,77] [Level _____ of evidence: I]

Tramadol	150 mg ~ 25 mg oral morphine	Use at <400 mg/d with or without acetaminophen. Used for moderate pain. Inhibits reuptake of norepinephrine and serotonin. Caution with concomitant antidepressant use.	[73]
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Table 3. Routes of Analgesic Medication Administration

Route	Agent	Comments	Reference(s)
Buccal	Fentanyl	Used primarily for breakthrough pain.	[78]
Epidural	Opioids, local anesthetics	Consider if inadequate analgesia or intolerable side effects with oral or intravenous analgesics.	[51]
Intramuscular injection	Opioids, acetaminophen, ketorolac	Typically avoided because of pain from injection.	[60]
Intranasal	Fentanyl	Onset faster than that of transmucosal fentanyl or oral morphine. Used for breakthrough pain.	[78]
Intrathecal	Opioids	Consider if inadequate analgesia or intolerable side effects with oral or intravenous analgesics.	[51]
Intravenous	Most strong opioids (except oxycodone) and some NSAIDs	Availability varies by world region.	[60]
Oral	Most opioids except fentanyl and buprenorphine	Most common and preferred method of administration.	[60]
Rectal	Morphine, methadone	Onset similar to that of oral; possibly better absorption. May be useful for pediatric and end-of-life patients.	[51]



Subcutaneous	Morphine, fentanyl, hydromorphone, ketoprofen, methadone	Benefit similar to that of intravenous; considered an alternative if no oral capacity.	[51 ,52 ,79]
Route	Agent	Comments	Reference(s)
Sublingual	Fentanyl, buprenorphine, concentrated morphine solution, methadone	Used primarily for breakthrough pain.	[67 ,78]
Topical	Lidocaine	Primarily application of topical anesthetics.	[60]
Transdermal	Fentanyl, buprenorphine	Efficacy similar to that of oral agents for moderate to severe pain in opioid-naïve patients.	[51]
Transmucosal	Fentanyl	Used primarily for breakthrough pain.	[78]

NSAIDs = nonsteroidal anti-inflammatory drugs.

ADVERSE EFFECTS OF OPIOID TREATMENTS

A]. OPIOID SIDE EFFECTS [93-97]

Addiction to opioids: It's essential to communicate with your healthcare provider about pain management and medication use. They monitor both pain levels and medication to balance effective pain control while minimizing the risk of addiction. If patient have any concerns or questions about using your prescribed pain medication safely, don't hesitate to discuss them with your healthcare provider. Remember, addressing pain early is often more effective, so adhering to your prescribed medication regimen is crucial.

Pain medication side effects: Absolutely, if patients experience confusion, drowsiness, or wooziness from your pain medication, it's crucial to discuss these side effects with your healthcare provider. They can provide guidance on adjusting your dosage or may suggest alternative medications to better manage your pain with fewer undesirable effects. Open communication about medication experiences helps tailor your treatment plan for optimal effectiveness and minimal side effects.

B]. OTHER MEDICATIONS=Healthcare providers may prescribe additional medications that may help with cancer pain or reduce the side effects of cancer pain medications. These medications may include:

a). Stimulants: It's important to note that while certain drugs, such as amphetamines, may help with opioid side effects, they also have the potential for high addiction risk. It's crucial to strictly adhere to your prescribed dose and avoid taking more than directed. Open communication with your healthcare provider about any concerns or experiences with side effects is essential to ensure safe and effective pain management.

b). Anticonvulsants: Absolutely, cancer and certain cancer treatments can indeed lead to nerve damage, resulting in neuropathic pain. Anticonvulsant medications like gabapentin (Gabarone®) and pregabalin (Lyrica®) are often prescribed to help alleviate this type of pain. These medications work to modulate nerve signals and can be effective in managing neuropathic pain associated with cancer. As always, it's essential to follow your healthcare provider's recommendations and communicate any concerns or changes in your condition.

c). Depression medications: Certainly, medications commonly used to treat depression, such as duloxetine (Cymbalta®, Drizalma®, Irenka®) and venlafaxine (Effexor®), can also be effective in managing nerve damage pain. These medications, known as serotonin-norepinephrine reuptake inhibitors (SNRIs), have analgesic properties that

make them valuable in addressing neuropathic pain associated with conditions like cancer or its treatments.

d). Corticosteroids: steroids like dexamethasone and prednisone are often prescribed to help manage inflammation and bone pain. They can have anti-inflammatory effects, making them useful in reducing pain associated with conditions like cancer. These medications are part of a comprehensive approach to pain management and are often prescribed based on the specific needs and conditions of the individual patient

e). Laxatives: opioids can indeed cause constipation as a common side effect. It's important for individuals taking opioids for pain management to be aware of this potential side effect. Healthcare providers often recommend preventive measures such as increased water intake, dietary fiber, and, if necessary, the use of stool softeners or laxatives. If constipation becomes a significant issue, it's crucial to communicate with your healthcare provider to explore appropriate solutions.

Adverse effects from opioids are indeed common and can pose challenges in achieving adequate pain control, as outlined in [Table 4]. It's important to note that not all adverse effects are solely attributed to opioids, and healthcare providers need to assess and consider various potential causes for any observed side effects. This comprehensive evaluation helps tailor pain management strategies to balance effectiveness and minimize undesirable effects. Examples of relevant factors include the following: [87]

- I. Symptoms from disease progression.
- II. Comorbid health conditions.
- III. Drug interactions (including adjuvant analgesics).
- IV. Clinical conditions such as dehydration or malnutrition.

Addressing adverse effects associated with opioids often involves considering several approaches, including aggressive management of the adverse effects, opioid rotation, or dose reduction. However, it's important to note that definitive recommendations may not be possible in all instances, as the most appropriate strategy can vary based on individual patient factors and the nature of the adverse effects. This underscores the importance of ongoing communication with healthcare providers to optimize pain management while minimizing side effects.

Table 4. Relative Prevalence of Opioid Adverse Effects by Duration of Use

Adverse Effect	Relative Prevalence		Comments	
	Acute Use	Chronic Use		
Cardiovascular				
Hypotension	+	+	Mostly with intravenous opioids.	
Central nervous system				
Sedation	+++	+	More common upon opioid initiation and dose increase.[88]	
Adverse Effect				
		Relative Prevalence		Comments
		Acute Use	Chronic Use	
Dizziness	++	+	[10]	
Delirium/hallucinations	+	+	[10]	
Impaired cognitive status	++	+	[10]	
Sleep disturbances	++	+	[10]	
Gastrointestinal				
Nausea	+++	+	Slow upward dose titration reduces risk. Lower rates with hydromorphone vs. morphine.[88,89]	
Vomiting	++	+	[10]	
Constipation	+++	+++	[40]	
Autonomic nervous system				
Xerostomia	+++	+	[10]	

Bladder dysfunction/urinary retention	+	+	[10]
Respiratory			
Respiratory depression	+	-	Extremely rare if used appropriately.[88]
Dermatologic			
Pruritus	++	-	More common with spinal analgesia.[88]
Miscellaneous			
Hyperalgesia	-	+	Observed more commonly with opioid-induced neurotoxicity. May be more common with morphine and hydromorphone.[91]
Opioid endocrinopathy/hypogonadism	-	+	[92 ,93]
Hypoglycemia	+	+	May be observed among patients on tramadol or methadone. More common among diabetics.

- The reported prevalence may differ on the basis of opioid choice, dose, route, and duration of use.
- Relative prevalence: (-) absent; (+) rare; (++) less common; (+++) common.
- Acute use defined as use for ≤2 weeks, as-needed use, and upon significant dose increase.
- Chronic use defined as consistent use for >2–3 months at stable doses.

ACETAMINOPHEN VS. IBUPROFEN: WHAT'S THE DIFFERENCE?[106]

How They Work ?

The exact mechanism by which acetaminophen and ibuprofen relieve pain and reduce fever is not fully understood, but the prevailing theory is that they both interfere with the production of prostaglandins in the body. Prostaglandins are chemicals that play a role in transmitting pain, generating fever, and promoting inflammation. Acetaminophen and ibuprofen block enzymes, known as COX enzymes, which are necessary for the production of prostaglandins.

It's worth noting that while acetaminophen primarily works in the brain, ibuprofen has effects throughout the body. As a result, acetaminophen helps reduce pain and fever, whereas ibuprofen provides the additional benefit of reducing inflammation and swelling at the site of an injury.

Risks and Benefits

The benefits of acetaminophen and ibuprofen are evident in their ability to reduce pain, lower fever, and, in the case of ibuprofen, decrease inflammation. However, it's crucial to consider the associated risks. Prolonged use of ibuprofen, in particular, can lead to decreased stomach protection from normal stomach acid, potentially causing ulcers and bleeding. Additionally, ibuprofen has the potential to harm the kidneys and contribute to high blood pressure, especially with large doses over an extended period.

As with any medication, it's essential to use them as directed and under the guidance of a healthcare professional to minimize the risk of adverse effects.

one of the primary risks associated with acetaminophen is the potential for liver damage, particularly when very high doses are taken. In

cases of an overdose, prompt medical attention is crucial to address the risk of liver failure, which, if not treated promptly, can be fatal. If there are concerns about taking too much acetaminophen, it's important to seek medical assistance immediately. Calling your local poison center, is a critical step for guidance and assistance in case of an overdose. It's always recommended to use medications, including over-the-counter ones, according to the recommended dosage and under the supervision of healthcare professionals.

The prolonged use of acetaminophen or ibuprofen to treat headaches can lead to a phenomenon known as rebound headaches. These headaches occur when there's a decrease in the levels of these medications in the blood, prompting

a cycle where individuals feel the need to keep taking these medicines to prevent the onset of headaches. Breaking this cycle often involves working closely with healthcare providers to develop a more sustainable and effective approach to headache management.

Correct usage of acetaminophen and ibuprofen at recommended doses for short durations is generally considered safe. It's crucial to adhere to the instructions on the bottle label or consult your doctor if you are uncertain about the proper dose. If there's a need for more prolonged use, or if you have any concerns, it's advisable to reach out to your medical provider for guidance. Open communication with healthcare professionals ensures safe and effective use of these medications.

Table 5. Pharmacokinetic and Pharmacodynamic Changes

Age-Related Physiological Change	Example of Affected Drugs
Decreased renal function	Increased accumulation of morphine metabolites
	Increased risk of NSAID-induced renal dysfunction
Increased body fat/decreased body water	Delayed elimination of lipophilic drugs such as methadone
Cachexia	Decreased fentanyl absorption from transdermal fentanyl patches [50]
Decreased hepatic function	Results in increased oral bioavailability and half-life of opioids
	– Decrease dose: hydromorphone, oxycodone
	– Increase dose interval: morphine, oxycodone
Reduced protein binding	Increased drug sensitivity/side effects
Reduced cytochrome P450 enzyme activity	Increased drug concentrations of fentanyl and methadone
Decreased gastrointestinal motility	Increased risk of opioid-induced constipation

LATEST UPDATES TO THIS SUMMARY (09/07/2023)

The PDQ cancer information summaries undergo regular reviews and are revised to incorporate the latest information. The following section outlines the most recent updates made to this summary as of the indicated date.

Pharmacological Therapies for Pain Control

information about a study that evaluated patients with head and neck cancer, indicating that White patients were significantly more likely than non-White patients to receive a new prescription for pain (citing Canick et al. as reference 95 and level of evidence III).

General Approaches to Pain Treatment

information about a study involving women with breast cancer, indicating that peripheral neuropathy correlated negatively with their quality of life.(cited Engvall et al. as reference 36 and level of evidence II).

Added Molassiotis et al. as reference 39.

Updated content to include symptom burden and alcohol intake as factors that increase the predisposition to neuropathy.

information about a genome-wide association study, noting that genetically determined African American ancestry was the most significant predictor of taxane-induced peripheral neuropathy (cited Schneider et al. as reference 41). Additionally, information about an observational study reporting that the impact of risk-factor profiles for chemotherapy-induced peripheral neuropathy may differ between racial and ethnic groups was added(cited Trendowski et al. as reference 42).

information about a Cancer and Leukemia Group B prospective observational study that

evaluated 2,450 patients with stage III colon cancer. The study found that increased severity of oxaliplatin-induced peripheral neuropathy (OIPN) may be linked to higher body mass index, lower physical activity, diabetes mellitus, and a longer planned duration of treatment. Notably, the study reported that Celecoxib and vitamin B6 intake did not attenuate OIPN.

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CANCER PAIN: THREE STEP ANALGESIC LADDER

The initiation of cancer pain management often involves a combination of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids, tailored to the current pain severity to achieve rapid and safe pain control.[107] Additionally, adjuvants like steroids, antidepressants, anticonvulsants, and bisphosphonates may be utilized based on the patient's unique situation.[107] The three-step analgesic ladder, a consistent aspect of the WHO cancer pain guidelines, provides a framework for developing an escalating pain management regimen. Studies have shown that with this approach, 70-80% of patients can find pain relief. [108]

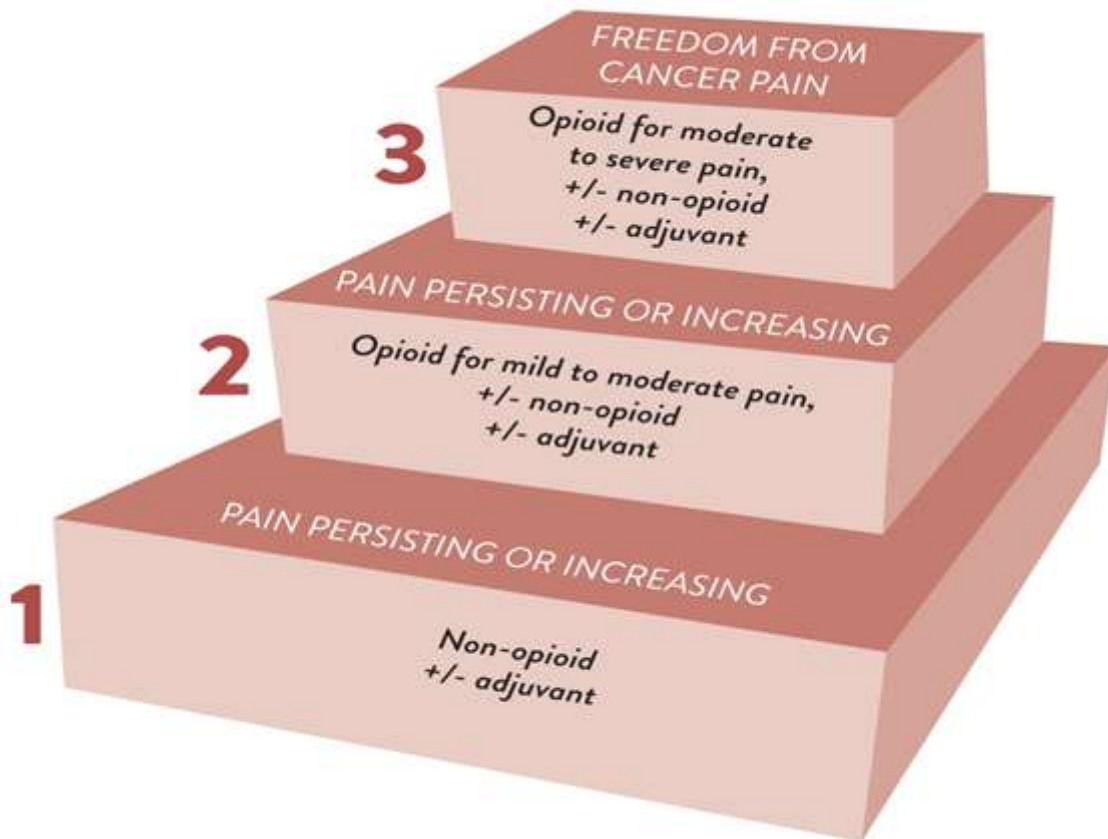


Figure 1. The Three-Step Analgesic Ladder Recommended By The World Health Organization. Sourced From WHO Guidelines For The Pharmacological And Radiotherapeutic Management Of Cancer Pain In Adults And Adolescents.

ADMINISTERING RAPID ONSET OPIOIDS FOR MANAGING BREAKTHROUGH CANCER PAIN: ADDRESSING DOSING CHALLENGES.

Cancer patients frequently experience varying levels of pain intensity. Breakthrough cancer pain (BTcP) is characterized as a temporary surge in pain intensity occurring on top of a baseline pain of moderate intensity in individuals regularly receiving analgesic treatment [110]. These patients typically maintain an acceptable level of pain control with their basal medication. Despite its variability, BTcP tends to have a rapid onset, is of moderate to severe intensity, and is relatively short-lived [111].

There are three primary categories of breakthrough cancer pain (BTcP) that have been recognized:

(a) Spontaneous Pain:

- This category involves pain that arises without any apparent precipitating event.

(b) Incident Pain:

- Incident pain is characterized by a clear precipitating cause or event. For instance, it may be

triggered by activities such as movement or specific actions.

(c) End-of-Dose Failure:

- This category is linked to therapeutic gaps resulting from a decline in the blood levels of analgesic medications administered at regular intervals. The pain occurs towards the end of the dosing cycle.

While the latter group doesn't precisely align with the conventional definition of BTcP, as it signifies inappropriate analgesia, it remains a clinical issue that should be addressed as BTcP. Another classification approach for BTcP involves considering the presence of volitional or precipitant factors, identified in over 50% of patients. Consequently, within each category, various subtypes can also be identified, acknowledging the diverse factors contributing to breakthrough pain in individual cases.

Prior surveys have consistently shown that breakthrough cancer pain (BTcP) is highly prevalent among patients with cancer pain. This

phenomenon is associated with more severe pain, increased pain-related distress, functional impairment, and a relatively poor quality of life [111]. Various surveys, utilizing different definitions and methodologies, have reported that 50–90% of cancer patients experiencing pain also encounter intermittent flares of their pain [110], [111], [112], [113], [114].

The prevalence figures for BTcP have been further substantiated by a comprehensive international survey, indicating a prevalence rate of approximately 65% [115]. This underscores the widespread nature of BTcP and its significant impact on the well-being and quality of life of individuals dealing with cancer-related pain.

Pharmacological treatment strategies for breakthrough cancer pain (BTcP) involve the implementation of primary therapies, the optimization of scheduled analgesia [116], and targeted treatment for BTcP [111], [112]. The focus of this review is to offer updated information on the use of opioids for addressing BTcP, with particular emphasis on the utilization of new rapid-onset opioids (ROOs). This approach aims to explore the efficacy and potential benefits associated with the latest advancements in rapid-onset opioids in managing the specific challenges posed by BTcP.

SECTION SNIPPETS

A. Oral opioids

The primary recommended approach for managing pain flares, such as those associated with breakthrough cancer pain (BTcP), involves providing supplemental doses of oral opioids in addition to the continuous analgesic medication. Current dosing recommendations for BTcP typically advise that the effective dose of BTcP medication should be a percentage of the patient's total daily opioid dose [117]. However, it's important to note that these recommendations, primarily derived from anecdotal experience, tend to favor the selection of an oral short-acting opioid at a dose proportionate to the total daily opioid intake.

B. Parenteral opioids

Given the urgent nature of pain relief requirements, routes of administration that facilitate rapid drug delivery are frequently preferred. A shorter onset of effect is typically achievable through parenteral administration of opioid analgesics. Intravenous morphine (IV-MO) has been identified as highly effective and safe, with only a low incidence of opioid-induced adverse effects observed, even with the

administration of large doses [118]. A recent confirmatory study involving a large sample of patients further validated the efficacy and safety of IV-MO in providing prompt and effective pain relief.

C. ROOs

Various technologies have been developed to facilitate rapid pain relief using potent opioid drugs like fentanyl, and these drugs are often delivered through non-invasive routes. The transmucosal administration of lipophilic substances has gained popularity in recent years due to its ability to produce a rapid clinical effect within 10–15 minutes after drug administration, all achieved through non-invasive means. It's important to note that not all drugs are suitable for transmucosal administration. Fentanyl, being a potent and highly lipophilic drug, aligns well with the requirements for effective transmucosal delivery.

Challenge Of Determining The Appropriate Dosage For Rapid-Onset Opioids (Roos)

The selection of the appropriate dose for rapid-onset opioids (ROO) prescribed as needed for breakthrough cancer pain (BTcP) is a topic of ongoing controversy. It is commonly recommended to titrate opioid doses for BTcP in controlled studies involving oral transmucosal fentanyl citrate (OTFC) and fentanyl buccal tablets (FBT). The reasons behind this recommendation are not clearly explained, especially considering that the presence of tolerance might suggest a dose proportional to those used for background analgesia.

One notable finding is the observed tolerance to adverse effects in patients chronically exposed to opioids, despite serum levels of opioids being within therapeutic ranges. This tolerance may contribute to the need for titration and individualized dosing in the management of breakthrough pain. Further research and clarification are needed to better understand the factors influencing the optimal dosage of ROOs for effective and safe relief of breakthrough cancer pain.

II. CONCLUSION

- A. Cancer pain can be from the cancer itself, or from cancer-related treatments
- B. Can be somatic, visceral, or neuropathic

- C. Negative effects of cancer-related pain can effect QOL, mortality
- D. Choose non-opioid / adjuvants carefully paying close attention to side effect profile
- E. Use WHO ladder guidelines when titrating pain medications
- F. Use long-acting opioids for chronic cancer pain
- G. Recognize "4th step" in WHO ladder and utilize your multidisciplinary resources

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