EPEC-O

Education in Palliative and End-of-life Care - Oncology

Participant's Handbook

Module 2

Cancer Pain Management

Accreditation Statement

Abstract

Most patients with cancer experience pain. Adequate assessment by a knowledgeable oncologist, often working closely with an interdisciplinary team, can relieve and control pain effectively. Data suggest that the earlier pain is controlled, the less severe it will become.

Pharmacologic management of nociceptive and neuropathic pain can be conceptualized along the 3 steps of the World Health Organization (WHO) 'analgesic ladder.' The addition of adjuvant analgesics is often critical to achieving an excellent outcome. Approaches have been developed to switch opioids while maintaining analgesia. Nonpharmacologic approaches may significantly increase the relief achieved.

Adequate pain control is possible in more than 90% of patients if the therapeutic approaches that are within the purview of all physicians are applied systematically. It is important to identify and address patient-related, profession-related, and system-related barriers to good pain control.

Key words

Addiction, adjuvant analgesics, adverse effects, barriers, cross-tolerance, equal analgesia, myths, neuropathic, nociceptive, non-opioid, opioid, opioid allergy, opioid excess, opioid overdose, pain, physical dependence, somatic, tolerance, visceral

Introduction

'Pain is a more terrible lord of mankind than even death itself.' [1]

Albert Schweitzer

Pain is a frequent problem in any oncology practice, whether associated with advanced illness or other acute or chronic conditions.[2,3] It is the physical symptom that patients and families fear most. Although oncologists now have effective treatments at their disposal, pain remains poorly assessed and treated. Lack of knowledgeable and experienced oncologists and myths about addiction continue to be significant barriers to good pain management and contribute unnecessarily to patient and family debilitation and suffering.

Objectives

After practicing the skills in this module, oncologists and will be able to:

- Compare and contrast nociceptive and neuropathic pain.

- Know steps of analgesic management.

- Know alternative routes of delivery.

- Demonstrate ability to convert between opioids while maintaining analgesia.

- Know use of adjuvant analgesic agents.

- Know adverse effects of analgesics and their management.

- Know principle methods of interventional pain management.

- List barriers to pain management.

Clinical case on trigger tape

H.G. is a 67-year-old mechanic who immigrated to the United States from Mexico 10 years ago. Fourteen months ago, H.G. presented with microcytic anemia, which soon led to a diagnosis of adenocarcinoma of the colon, Duke stage C. Treatment included bowel resection and adjuvant chemotherapy. During his treatment, H.G. was relatively asymptomatic. Subsequently, he noted pain in his leg. Imaging studies revealed lesions in the liver and right femur. A bone biopsy confirmed the diagnosis of metastatic adenocarcinoma. It has been 6 weeks since H.G. learned the news of the cancer's recurrence.

General principles

This module focuses on the assessment and management of physical pain. This is not to imply that the other components of suffering (other physical, psychological, social, spiritual, or practical issues) are diminished in their importance.

The process of pain management starts with adequate assessment of the pain: its nature, cause, personal context including psychological, social, spiritual, and practical issues, and underlying pathophysiology. Management includes appropriate pharmacologic and non-pharmacologic interventions; education of the patient, family, and all caregivers about the plan; ongoing assessment of treatment outcomes; and regular review of the plan of care.

Use of other members of the interdisciplinary team perhaps including the nurse, social worker, pharmacist, chaplain, physiotherapist, occupational therapist, child life specialist, etc, is often key to adequate pain management. Flexibility is essential—successful plans are tailored to the individual patient and family. When the plan is not effective at controlling the patient's pain, ask for help from colleagues with more expertise.

Assessment

Pain management requires adequate assessment. Its absence is the leading reason for poor pain management. Comprehensive Assessment is discussed in EPEC-O Module 1.

The gold standard of assessing pain is to believe the patient. For cognitively intact patients, assess location, radiation, quality, intensity, factors that exacerbate or relieve the pain, and temporal aspects such as whether it is continuous or paroxysmal, as well as its duration and meaning to the patient. Spontaneous pain of short duration could be the paroxysmal firing of a neuroma. Back pain that occurs only with weight bearing could

indicate a spinal bony metastasis. Furthermore, whether the pain is directly or indirectly related to the cancer, related to therapy, or unrelated should be assessed. These insights may help elucidate the pathophysiology that underlies the pain and may also direct the therapy.[4,5]

Quantify pain intensity; ask the patient to rate the pain. This rating can be accomplished with a verbal rank on a scale of 1-10 where 10 is the worst pain, visual analog scales where a patient indicates pain with a mark on a 100 mm line delimited by descriptors such as no pain and worst possible pain at either end, or other validated means. Whereas acute pain is accompanied by signs of adrenergic stimulation such as tachycardia and hypertension, chronic pain is not associated with these autonomic responses even though the patient remains in pain. Thus, lack of observable vital sign changes does not rule out pain or indicate a patient is malingering.

Together with a careful physical exam and select laboratory and imaging studies, in which the benefits of the study outweigh the burdens, it is usually possible to identify the relevant pathophysiology leading to a pain state. While this module focuses on physical pain, any particular pain syndrome happens in a whole person. The concept of 'total pain' emphasizes that there may be non-physical causes of pain as well. Psychologic (eg, depression), social (eg, familial estrangement), and spiritual or existential (eg, loss of meaning in life) factors can exacerbate pain.[6] It may not be possible to control pain successfully without also addressing these other sources of suffering.

Pathophysiology

Although some think of pain as a homogeneous sensory entity, several types and subtypes have been described. The neurobiological mechanisms responsible for these different pains provide insight into treatment.[7] Pain can be acute or chronic. Acute pain is usually related to an easily identified event or condition. Resolution is anticipated within a period of days or weeks. Chronic pain may or may not be related to an easily identified pathophysiologic phenomenon and may be present for an indeterminate period.

Acute and chronic pain may be conceptualized as either nociceptive or neuropathic in origin.[2] A broad description of the predominating pain pathophysiology can usually be inferred through the description, physical findings, and the results of laboratory tests and imaging studies. The International Association for the Study of Pain (IASP) has published precise definitions and made them available on their Web site, www.pslgroup.com.

Nociceptive pain

Nociceptive pain involves *direct stimulation of nociceptors that detect mechanical, chemical, and thermal stimuli and mediate nociceptive pain*. They transmit this information along normal pathways to be perceived in the brain. Nociceptive pain can be further subdivided into somatic and visceral pain. Somatic pain, mediated by the somatic

nervous system, subserves skin, bone, and muscle. Pain localization is precise and is often described as sharp, aching, or throbbing. Visceral pain, mediated by the autonomic nervous system, subserves internal structures such as the gastrointestinal tract. It is typically difficult to localize or describe, and sometimes characterized as crampy.
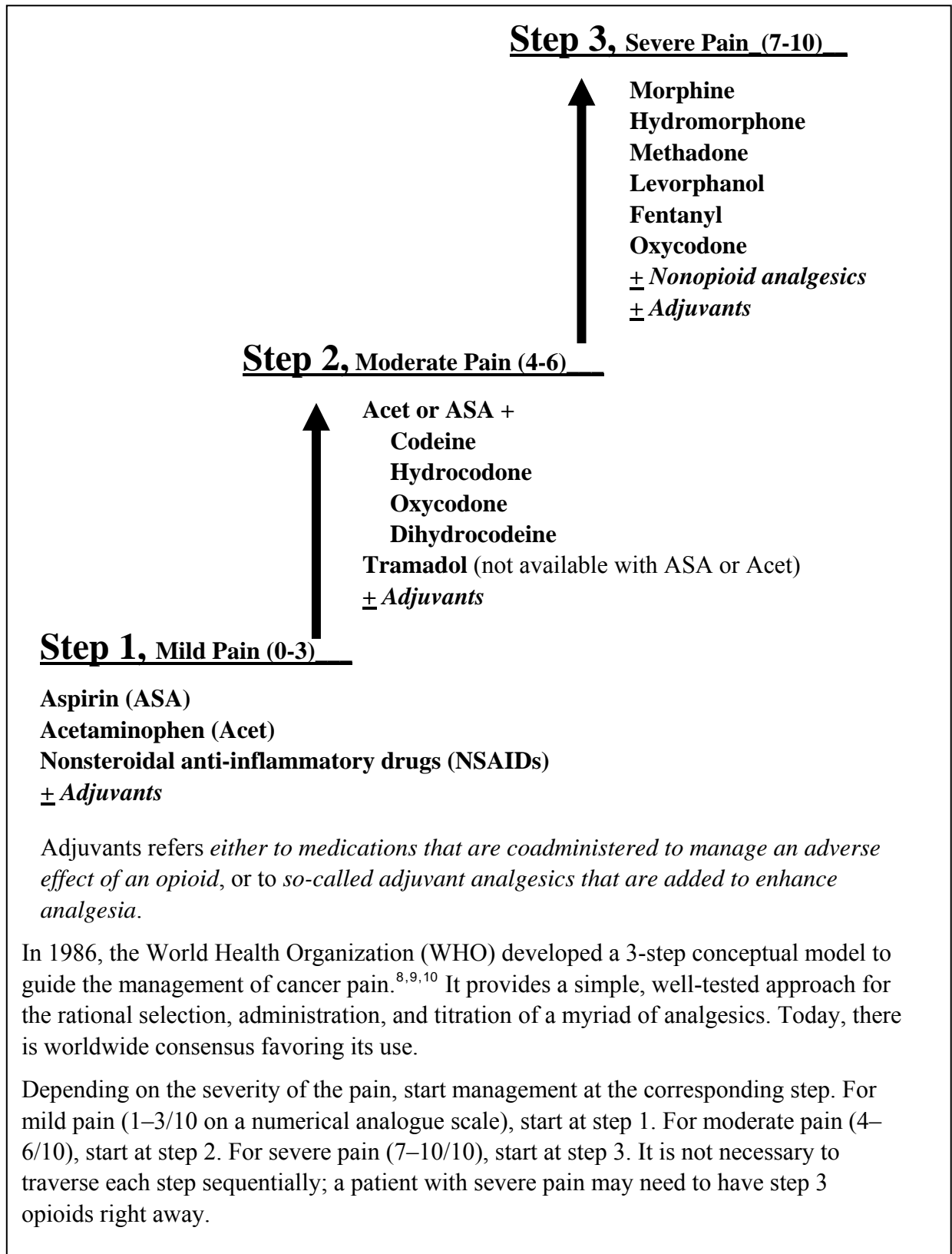
Neuropathic pain

Neuropathic pain has been defined as *a primary lesion or dysfunction of the nervous system*.[3] It can be either peripheral or central. The nerves themselves may be damaged by ischemia, compression, infiltration, metabolic injury, or transection. For example, post-thoracotomy syndrome may be due to the formation of a neuroma caused by aberrant healing after surgical transaction.[4] However, neuropathic pain may also involve dysfunction of the nervous system. For example, repetitive nociceptive pain stimuli can create a condition where spinal cord neurons have increased sensitivity in a process called central facilitation. Although the nerves themselves are undamaged, an abnormal signaling system has been set up where a given noxious stimulus receives a larger response than normal and non-noxious light touch can stimulate pain pathways. This facilitated sensory state at least partially explains the neuropathic clinical phenomenon of allodynia, where light touch, such as the pressure from a bed sheet, causes pain. The N-methyl-D-aspartate (NMDA) receptor is thought to be involved in setting up this abnormal pathway.[5] Thus, there is at least a subset of neuropathic pain that can develop from repetitive nociceptive pain without structural damage to the nerves themselves. Preliminary evidence suggests that, if the initial nociceptive pain impulses are controlled, these neurological changes can be prevented. Neuropathic pain is often described as burning, tingling, numbness, shooting, or electric-like.

Patients tend to describe neuropathic pain with words like burning, tingling, numbness, shooting, stabbing, or electric-like feelings. Although neuropathic pain may respond well to opioids, adjuvant analgesics (tricyclic antidepressants, anticonvulsants, antiarrhythmics, etc.) are often required in combination with opioids to achieve adequate relief.

Management

While the diagnosis and treatment of the underlying cause of any pain is an important part of the medical treatment plan, there is no reason to delay the use of analgesics. It is not appropriate to withhold pain management until the investigations and treatment of the underlying disease are complete, or other criteria are met. Although research is not yet conclusive, unmanaged pain may lead to changes in the nervous system that could reduce its responsiveness to treatment. Equally important, unrelieved pain can have a devastating psychological effect on the individual and family. Combine the use of primary therapies directed against the source of pain (eg, radiation for a neoplasm) with approaches to manage the pain.

WHO 3-Step Ladder

Step 3, Severe Pain_(7-10)__

Morphine
Hydromorphone
Methadone
Levorphanol
Fentanyl
Oxycodone
+ *Nonopioid analgesics*
+ *Adjuvants*

Step 2, Moderate Pain (4-6)___

Acet or ASA +
  Codeine
  Hydrocodone
  Oxycodone
  Dihydrocodeine
Tramadol (not available with ASA or Acet)
+ *Adjuvants*

Step 1, Mild Pain (0-3)__

Aspirin (ASA)
Acetaminophen (Acet)
Nonsteroidal anti-inflammatory drugs (NSAIDs)
+ *Adjuvants*

Adjuvants refers *either to medications that are coadministered to manage an adverse effect of an opioid,* or to *so-called adjuvant analgesics that are added to enhance analgesia.*

In 1986, the World Health Organization (WHO) developed a 3-step conceptual model to guide the management of cancer pain.[8,9,10] It provides a simple, well-tested approach for the rational selection, administration, and titration of a myriad of analgesics. Today, there is worldwide consensus favoring its use.

Depending on the severity of the pain, start management at the corresponding step. For mild pain (1–3/10 on a numerical analogue scale), start at step 1. For moderate pain (4–6/10), start at step 2. For severe pain (7–10/10), start at step 3. It is not necessary to traverse each step sequentially; a patient with severe pain may need to have step 3 opioids right away.

Placebos

Some physicians have advocated the use of placebos to see if patients are really in pain. While 30-70% of patients will appear to experience some response, there is no ethical or scientific basis for the use of placebos to assess or treat pain. The Agency for Health Care Policy and Research (AHCPR), American Pain Society (APS), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), and the American Nursing Association (ANA) have all issued position statements to this effect.

Pharmacologic approaches to pain management

Effective treatment requires a clear understanding of the pharmacology, potential impact, and adverse effects associated with each of the analgesics prescribed, and how these may vary from patient to patient. Information about the prescribing of individual analgesics is summarized in the Medication Tables at the end of the EPEC-O materials.

Step 1 analgesics

The non-opioid analgesics that characterize step 1 of the WHO ladder all have a ceiling effect to their analgesia (a maximum dose past which no further analgesia can be expected).

Acetaminophen

Acetaminophen is an effective step 1 analgesic. It may also be a useful coanalgesic in many situations, including headache. Its site and mechanism of action are not known. It does not have significant anti-inflammatory effects and is presumed to have a central mechanism. Its metabolism in the liver creates a reactive metabolite that can cause liver damage if glutathione stores are depleted.[11] Chronic doses > 4.0 g 24 h or acute doses > 6.0 g 24 h are not recommended for this reason. Hepatic disease or heavy alcohol use increases the risk further.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin) are effective step 1 analgesics. They may also be useful coanalgesics. The doses to achieve analgesia may be lower than the doses to be antiinflammatory. They work, at least in part, by inhibiting cyclo-oxygenase (COX), the enzyme that converts arachidonic acid to inflammatory prostaglandins.

NSAIDs decrease the noxious stimulus normal nociceptors receive. Moreover, there is a group of silent nociceptors that only fire in an inflammatory milieu.[12] The same noxious stimulus in the absence of inflammation would fail to cause these silent nociceptors to fire. Finally, cyclo-oxygenase has also been identified in spinal cord neurons where it appears to play a role in setting up the dysfunctional signaling pattern involved in

neuropathic pain.[13] These observations help explain why NSAIDs may be so useful in conjunction with opioids for severe pain.

There are several classes of NSAIDs. Some patients respond better to one class of NSAIDs than to another, and serial 'n of 1' trials may be needed to find one that is efficacious for a given patient. Extended-release products are likely to enhance compliance and adherence. Intravenous formulations are also available for at least one of the NSAIDs (ketorolac). Details of individual drugs are listed in the Medication Tables at the end of the EPEC-O materials.

NSAIDs can have significant adverse effects that include gastropathy, renal insufficiency, and platelet inhibition.[14] These side effects may be explained, in part, by the fact that cyclo-oxygenase exists in 2 forms–a constitutive form, COX-1, and a form that is inducible under conditions of inflammation, COX-2. There are COX-2 selective NSAIDs and non-selective NSAIDs that target both forms. Whereas renal insufficiency is a risk of both non-selective and COX-2 selective NSAIDs, the risk of gastropathy and platelet inhibition is significantly decreased with COX-2 selective NSAIDs.[15] It is possible to ameliorate the gastropathy associated with non-selective NSAIDs by using protective agents such as misoprostol, or proton pump inhibitors.[15] Although COX-2 selective NSAIDs have a better side effect profile, they are expensive and have not been well studied in the end of life population, and may provide less analgesia than nonspecific NSAIDs.

Step 2 and 3 analgesics

Step 2 and 3 analgesics involve opioids that act at opioid receptors. These receptors are found both peripherally and centrally, but the central receptors in the spinal cord and brain are most important for controlling pain. Opioid receptors affect the intracellular levels of potassium and calcium modifying a nerve's threshold for firing and propensity to release neurotransmitters. Opioids are the first-line therapy for moderate to severe pain in nociceptive, neuropathic, and mixed pain syndromes. However, for severe neuropathic pain, opioids alone are often insufficient[16] and must be combined with adjuvant analgesics as will be discussed later. In fact, an important clinical clue that there may be a neuropathic component to a pain syndrome is when high dose opioids are unsuccessful in controlling pain.

The step 2 medications include tramadol and combination formulations of acetaminophen or aspirin with opioids. Tramadol, in addition to having weak activity at opioid receptors, also affects norepinephrine and serotonin levels.[17] Although the exact mechanism is unknown, the non-opioid effects of tramadol may mediate its efficacy for neuropathic pain.[18] Although tramadol has relatively weak affinities at its sites of action, synergism of its activities may allow for lower doses to be used in comparison with other weak opioids.[19] Thus, for moderate pain, tramadol use may result in analgesia with less opioid side effects such as constipation. Commonly available opioids available as combination medications include codeine, oxycodone, and hydrocodone. The opioids combined with

acetaminophen or aspirin are limited in dosage due to their non-opioid components. For example, combinations containing acetaminophen 500 mg would be limited to ≤8 tablets per day due to the risk of hepatotoxicity.

The step 3 pure opioids do not share this limitation, and in fact they have no theoretical ceiling for efficacy or end-organ toxicity.[20,21] They can be titrated to effect limited only by adverse effects. Commonly prescribed agents in this step include morphine, oxycodone, hydromorphone, levorphanol, fentanyl, and methadone.

Opioid pharmacology

Opioids, codeine, hydrocodone, hydromorphone, morphine, oxycodone, etc., all follow first-order kinetics and pharmacologically behave very similarly. They reach their peak plasma concentration (Cmax) approximately 60 to 90 minutes after oral (including enteral feeding tube) or rectal administration, 30 minutes after subcutaneous or intramuscular injection, and 6 minutes after intravenous injection.[22,23]

The analgesia associated with each opioid has a half-life ($t_{1/2}$) that depends both on the rate of liver metabolism and its rate of renal clearance. Except for methadone, that has a half-life that ranges from 15 to 40 hours, codeine, hydrocodone, hydromorphone, morphine, oxycodone, and their metabolites all have effective half-lives of approximately 3 to 4 hours when renal clearance is normal.[24] When dosed repeatedly, their plasma concentrations approach a steady state after 4 to 5 half-lives. Thus, steady-state plasma concentrations are usually attained within a day.

Pharmacologic dosing curves after a single opioid dose

Curves vary based on the route of administration
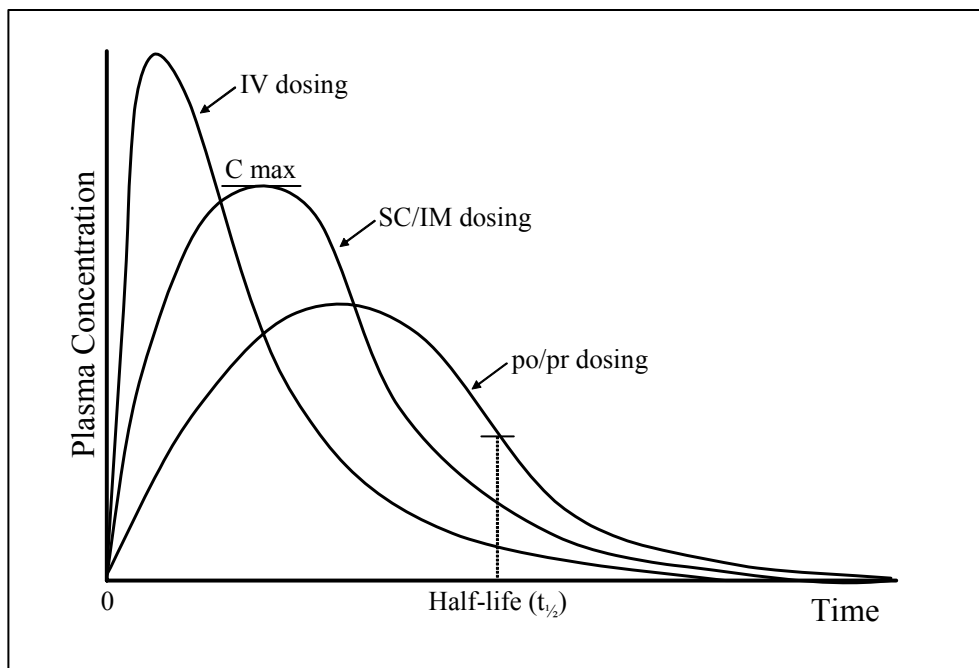
Routine oral dosing–immediate-release opioid preparations

If an immediate-release oral opioid is selected and the pain is continuous or nearly so, give the medication q 4 h. For example, an opioid naïve patient who is in significant pain could be started on morphine 15 mg orally scheduled every 4 hours. Given this dosing, the total 24-hour dose of morphine a patient would receive is 90 mg. The best possible pain control for the dose will be achieved within a day (once steady state has been reached). Provide the patient with access to PRN doses of the same medication that can be used should breakthrough pain occur (rescue dose). This is covered in the next section.

If pain remains uncontrolled after 24 hours, increase the routine dose by 25-50% for mild to moderate pain, by 50-100% for severe to uncontrolled pain, or by an amount at least equal to the total dose of rescue medication used during the previous 24 hours. Do not wait any longer. Delays only prolong the patient's pain unnecessarily.

If pain is severe and uncontrolled after 1 or 2 doses (eg, crescendo pain), increase the dose more quickly. Observe the patient closely until the pain is better controlled.

Guidelines for initial dosing of morphine are given in the Appendix.

Routine oral dosing–extended-release and long half-life opioid preparations

Increasingly, oral extended- or sustained-release formulations of the commonly used opioids are becoming widely available for routine usage. Less frequent dosing with either these preparations or opioids with long half-lives (eg, methadone, $t\frac{1}{2} \approx 12$–24 hours, sometimes longer) is likely to improve patient compliance and adherence.

Extended- or sustained-release opioid tablets are specifically formulated to release medication in a controlled fashion over 8, 12, or 24 hours (depending on the product). They must be ingested whole, not crushed or chewed. Extended-release capsules containing time-release granules can be swallowed whole, or the granules can be mixed with fluid and flushed down a feeding or other tube into the upper GI tract. Best possible pain control for the dose will be achieved within 2 to 4 days (once steady state has been reached). Doses should not be adjusted any more frequently than once every 2 to 4 days.

For example, instead of giving 15 mg every 4 hours, the patient would receive 45 mg extended-release morphine q 12 hours.

Extended-release preparations may avoid a potential problem with short acting opioids called the bolus effect. This phenomenon is related to peak and trough effects of dosing. Peak levels attained after taking an immediate release preparation may be high enough to induce side effects such as lethargy, but trough levels before the next dose may be insufficient to keep pain under control. Extended-release opioids or continuous infusions of opioids avoid these pitfalls by smoothing out peak and trough extremes.

Methadone has a long and variable half-life. Although the half-life usually approaches a day or longer, the effective dosing interval for analgesia is usually as frequently as q 8 h;

it is often q 6 h and sometimes even q 4 h. Given the variability of methadone's half-life and the unexpected potency that this medication often demonstrates, it is prudent to increase the maintenance dose only every 4 to 7 days, or less often, if possible. Treat uncontrolled pain with breakthrough doses as needed.

Breakthrough dosing

Transitory flares of pain, called 'breakthrough pain,' can be expected both at rest and during movement. When such pain lasts for longer than a few minutes, extra doses of analgesics, i.e., breakthrough or rescue doses, will likely provide additional relief. To be effective and to minimize the risk of adverse effects, consider an immediate-release preparation of the same opioid that is in use for routine dosing. When methadone or transdermal fentanyl is used, it is best to use an alternative short-acting opioid, eg, morphine or hydromorphone, as the rescue dose. Oral immediate-acting fentanyl is also available.

For each breakthrough dose, offer 5-15% of the 24-hour dose. As peak analgesic effect correlates with peak plasma concentration (Cmax), a breakthrough dose can be offered once Cmax has been reached. Therefore, morphine, oxycodone, codeine, and hydromorphone can be administered every 1 hour if administered orally, or possibly less frequently for frail patients, every 30 minutes if administered subcutaneously, or intramuscularly, and every 10 to 15 minutes if administered intravenously. Longer intervals between breakthrough doses only prolong a patient's pain unnecessarily.

For example, for the patient who was receiving 45 mg every 12 hours for a total of 90 mg morphine daily, the breakthrough dose would be 10-15 mg PO q 1 h.

Metabolism and clearance concerns

Opioids are metabolized in the liver and 90-95% excreted by the kidney. Their metabolic pathways do not become saturated. For example, the liver conjugates morphine to an active metabolite, morphine-6-glucoronide, and an inactive metabolite, morphine-3-glucuronide, that must be cleared renally.[20] There is evidence that other opioids such as codeine, hydrocodone, hydromorphone, and fentanyl also have active metabolites. Only methadone is excreted unchanged.

When dehydration or acute or chronic renal failure impairs renal clearance, the dosing interval for morphine must be increased, or the dosage size decreased, to avoid excessive accumulation of active drug. If urine output is minimal (oliguria) or none (anuria), stop routine dosing and administer morphine only 'as needed.' This is particularly important when patients are dying.

Opioid metabolism is not usually affected by extensive liver metastases. However, if hepatic function becomes severely impaired by hep

atitis or there is clinical liver failure, increase the dosing interval or decrease the dose.

Not recommended

Not all analgesics available today are recommended for acute or chronic dosing.

Meperidine is poorly absorbed orally and has a short half-life of approximately 3 hours. Its principal metabolite, normeperidine, has no analgesic properties of its own, has a longer half-life of about 6 hours, is renally excreted, and produces significant adverse effects when it accumulates, such as tremulousness, dysphoria, myoclonus, and seizures. The routine dosing of meperidine q 3 h for analgesia leads to unavoidable accumulation of normeperidine and exposes the patient to unnecessary risk of adverse effects, particularly if renal clearance is impaired. Consequently, meperidine is not recommended for routine dosing.

Propoxyphene is typically administered at doses that produce relatively little analgesia. Dose escalation could lead to accumulation of a toxic metabolite.

The mixed opioid agonist-antagonists, such as pentazocine, butorphanol, nalbuphine, and dezocine, should not be used in the patient already taking a pure agonist opioid (codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone). If used together, competition for the opioid receptors may cause a withdrawal reaction. Further, agonist-antagonists are not recommended as routine analgesics, as their dosing is limited by a ceiling effect. The use of pentazocine and butorphanol is associated with a relatively high risk of psychotomimetic adverse effects.

Addiction

The perception that the administration of opioid analgesics for pain management causes addiction is a prevalent myth that inhibits adequate pain control. Confusion about the differences between addiction, tolerance, and physical dependence is in part responsible.

Addiction, as the term is now used, is a complex phenomenon. Its hallmark is psychological dependence on drugs and a behavioral syndrome characterized by compulsive drug use and continued use, despite harm. Care must be taken to differentiate a true addiction (substance use disorder) from pseudoaddiction due to undertreatment of pain, behavioral/family/psychological dysfunction, and drug diversion with criminal intent.

Pharmacologic tolerance is the reduced effectiveness of a given dose of medication over time. Tolerance to side effects is observed commonly and is favorable. Tolerance to analgesia is rarely significant clinically when opioids are used routinely. Doses may remain stable for long periods if the pain stimulus remains unchanged. When increasing doses are required; suspect worsening disease rather than pharmacologic tolerance.

Physical dependence is the result of neurophysiologic changes that occur in the presence of exogenous opioids. Similar outcomes occur in the presence of exogenous hormones and other medications (beta-blockers, alpha-2 agonists, etc). Abrupt opioid withdrawal may result in an abstinence syndrome characterized by tachycardia, hypertension, diapho-

resis, piloerection, nausea and vomiting, diarrhea, body aches, abdominal pain, psychosis, and/or hallucinations.

Physical dependence is not the same as addiction. Physical dependence is not evidence of addiction. Its presence does not mean that opioids cannot be discontinued. If the pain stimulus decreases or disappears, opioid doses usually can be reduced in decrements of 50% or more every 2 to 3 days, and finally stopped. If the dose is lowered too quickly and abstinence symptoms occur, a transient increase in the opioid dose, treatment with clonidine, or a small dose of a benzodiazepine (eg, lorazepam) may be necessary to settle distressing symptoms.

To manage pain effectively, physicians will need to educate patients, families, and other professionals about the inappropriate fear of addiction. Opioids by themselves do not cause psychological dependence. Addiction is a rare outcome of pain management when there is no history of substance abuse.

Since patients with histories of substance abuse can also develop significant pain, they deserve compassionate treatment of their pain when it occurs. Most will need to adhere to strict dosing protocols, and contracting may become necessary. Physicians who are un-familiar with these situations may need the help of specialists in pain management and/or addiction medicine.

Pain poorly responsive to opioids

If dose escalation results in adverse effects, there are a few options. More sophisticated adverse effect therapy, such as a psychostimulant, may help sedation. An alternate route of administration or a different opioid may be effective, without some of the side effects. An adjuvant analgesic may help reduce the amount of opioid required. Finally, consider a non-pharmacologic approach. These possibilities are discussed in parts 2 and 3, which follow.

Ongoing assessment

If pain control is inadequate, the dose of analgesics should be increased until pain relief is achieved or unacceptable adverse effects occur. In contrast with acetaminophen and the NSAIDs, there is no maximum dose of a pure agonist opioid. If adverse effects become intolerable, an alternative analgesic or route of administration may be more effective at controlling the pain without producing the same adverse effects. Some patients will also experience less pain spontaneously or with changes in their underlying cause. If the pain decreases or disappears, analgesic doses may need to be reduced or discontinued.

If patients have good pain control on stable doses of an opioid, and are not experiencing any adverse effects (especially drowsiness), it is safe to drive a car.

Alternative routes of administration

In general, the oral route is the least invasive, most convenient route for administering opioids on a routine basis. However, selected patients may benefit from other routes of administration if oral intake either is not possible (due to vomiting, dysphagia, or eso-phageal obstruction) or causes uncontrollable adverse effects (nausea, drowsiness, or confusion).

Enteral feeding tubes provide alternatives for bypassing gastroesophageal obstructions. They deliver the medications to the stomach or upper intestine where the medications behave pharmacologically as though they had been ingested orally.

Transmucosal (buccal mucosal) administration of more concentrated immediate-release liquid preparations provides a similar alternative, particularly in the patient who is unable to swallow. This route is particularly effective for patients who are dying.

Oral transmucosal fentanyl citrate is a new formulation of fentanyl, in a candy matrix on a stick, that is approved for the treatment of breakthrough pain. To date, experience with the formulation is very limited (US only).

Rectal administration of immediate or extended-release rectal preparations behave phar-macologically like related oral preparations.[25] This route may be very effective if oral intake is suddenly not possible, although many patients do not like this route for continuous administration.

Transdermal patches present an effective alternative route of administration for patients receiving stable routine opioid dosing. Currently, transdermal patches are only manufactured for fentanyl. Transdermal patches behave quite differently from other extended-release formulations. Steady-state equilibrium is established between the medication in the patch, a subdermal pool that develops, and the patient's circulation. On average, best possible pain control is achieved within 1 dosing interval (i.e., 3 days) with peak effect at about 24 hours. The effect usually lasts for 48 to 72 hours before the patch needs to be changed. Care must be taken to ensure that patches adhere to the patient's skin (avoid hairy areas) and do not lift off with bathing or sweating.

Parenteral administration using injection or infusion can be very useful in selected pa-tients. When renal function is normal, provide routine parenteral bolus doses every 3 hours and adjust the dose every 12 to 24 hours once steady state is reached. Doses are effectively the same for subcutaneous, intravenous, or intramuscular administration. If a parenteral route will be used for some time, continuous infusions may produce a more constant plasma level, reduce the risk of adverse effects, be better tolerated by the patient, and require less intervention by professional staff. Patient-controlled analgesia has been shown to be both effective and well tolerated by patients.

While intravenous infusions may be preferable if intravenous access is already estab-lished and in use for other medications, all opioids available for parenteral use may be administered subcutaneously without the discomfort associated with searching for an IV

site or the same risk of serious infection. Either 25- or 27-gauge needles can be used for both bolus dosing and infusions. The needles can be left in place for 7 days or more as long as there is no sign of infection or local irritation. Family members can be taught to change them.

Intramuscular injections are not recommended. Intermittent subcutaneous doses are much less painful and just as effective.

Intraspinal opioids, epidural or intrathecal, may be useful in selected patients who have pain in the lower part of their body, or pain that is poorly responsive to routine systemic opioid therapy. Intraspinal delivery allows much lower doses of opioids to be used and consequently reduces systemic side effects. Opioids such as morphine, hydromorphone, or fentanyl are used. They are typically combined with a local anesthetic and/or an alpha-2-adrenergic agonist. Other invasive chemical and surgical neurolytic procedures are sometimes used in specific pain syndromes. A specialist who is knowledgeable about their specific indications and pharmacology, and who is skilled in their delivery, is usually required to administer them.

Bolus effect

As the total dose of opioid in the bloodstream changes, some patients may experience drowsiness ½ to 1 hour after ingestion of a dose of medication as the plasma level peaks followed by pain just before the next dose is due as the plasma level falls. This syndrome, known as the 'bolus effect,' can only be resolved by switching to an extended-release formulation (oral, rectal, or transdermal) or a continuous parenteral infusion to reduce the swings in the plasma concentration after each dose.

Changing routes of administration of opioids

When changing routes of administration, an equianalgesic table is a useful guide for initial dose selection. Significant first-pass metabolism necessitates larger oral or rectal doses to produce analgesia equivalent to parenteral doses of the same opioid. Equivalent dosing recommendations represent consensus from limited available evidence, so they are guides only, and individual patients may require doses to be adjusted. Tables, such as the one indicated here, are clinically convenient and easy to use. Large between-patient variability makes firm ratios elusive.

CLINICAL GUIDE FOR CHANGING OPIOID ANALGESICS		
ORAL/RECTAL DOSE (MG)	ANALGESIC	PARENTERAL DOSE (MG)
150	Codeine	50
150	Meperidine	50
150	Tramadol	-
15	Hydrocodone	–
15	Morphine	5
10	Oxycodone	–
3	Hydromorphone	1
2	Levorphanol	1
–	Fentanyl	0.05

A clinical guide for changing opioid analgesics such as this one, adapted with permission from Levy, can be used on the horizontal axis to switch routes of administration and on the vertical axis to switch between opioids.[26]

Changing opioids

When converting to or from transdermal fentanyl patches, published data from the manufacturer suggest that a 25-µg patch is equivalent to 45 to 135 mg of oral morphine per 24 hours. However, published clinical experience suggests that most patients will use the lower end of the range of morphine doses (i.e., for most patients, 25 µg is about equivalent to 45 to 60 mg of oral morphine per 24 hours).[27,28]

Opioid rotation

For reasons that remain obscure, two or three different opioids may need to be successively tried until a drug that provides good analgesia with minimal adverse effects is found for an individual patient.[29]

Opioid cross-tolerance

While pharmacologic tolerance may develop to the opioid in use, tolerance may not be as marked relative to other opioids.[30] Incomplete cross-tolerance is likely due to subtle differences in the molecular structure of each opioid and the way each interacts with the patient's opioid receptors. Consequently, when switching opioids, there may be differences between published equianalgesic doses of different opioids and the effective ratio for a given patient. Start with 50-75% of the published equianalgesic dose of the new opioid to compensate for incomplete cross-tolerance and individual variation, particularly if the patient has controlled pain. If the patient has moderate to severe pain, do not reduce the dose as much. If the patient has had adverse effects, reduce the dose more.

An important exception is methadone, which appears to have higher than expected potency during chronic dosing compared with published equianalgesic doses for acute dosing.[31,32,33] Because methadone has both opioid and NMDA receptor antagonistic effects, the apparent equianalagesic ratio changes based on dose.

Methadone

Daily morphine equivalent dose (mg / 24 hr PO)	Conversion ratios		
	Morphine PO		Methadone PO
<100	3	:	1
101 – 300	5	:	1
301 – 600	10	:	1
601 – 800	12	:	1
801 – 1,000	15	:	1
>1,001	20	:	1

Methadone SC Dosing

1) Convert from daily morphine equivalent dose PO / 24 hr
   to methadone PO dose / 24 hr using the Methadone PO Dosing Table above.

2) Then ÷ 3 to convert to Methadone SC Dose / 24 hr.

Adjuvant analgesics

Adjuvant analgesics (or coanalgesics) are *medications that, when added to primary analgesics, further improve pain control*. They may themselves also be primary analgesics (eg, tricyclic antidepressant medications for postherpetic neuralgia). They can be added into the pain management plan at any step in the WHO ladder.

The classes of medication used to treat neuropathic pain include anticonvulsants, antidepressants, NMDA-receptor antagonists, local anesthetics, and alpha-2-adrenergic agonists. There is no clear consensus on what adjuvant category to utilize first, but many clinicians choose to initially prescribe an anticonvulsant or antidepressant medication.

Anticonvulsants

The molecular mechanism by which anticonvulsants produce analgesia is not clear, but presumably is related to their effects on neuronal discharge. Gabapentin has emerged as the most common initial therapy. Studies have shown it be efficacious in the control of post-herpetic neuralgia and diabetic neuropathic pain.[34,35] Levels need not be followed and it has a relatively safe side effect profile. The most troublesome side effect is lethargy. This symptom can usually be controlled by 'starting low and going slow' in titration. Doses as low as 300 mg per day may be effective, but often 900 mg per day is the typically effective dose. If necessary, doses can be gradually increased to a level of 3600 mg/day limited by efficacy or side effects. Clonazepam is also effective with a relatively good side effect profile.[36] Other anticonvulsants such as carbamazepine and valproic acid are effective but require monitoring of levels and monitoring for signs of organ toxicity.[37] Newer anticonvulsants such as lamotrigine also seem to be effective in early clinical studies.[38] If one anticonvulsant is not effective, it is rational to try another one.

Antidepressants

The tricyclic antidepressants are the best studied antidepressant class that shows efficacy in neuropathic pain. The pain effect has been separated from the antidepressive effect.[39] Doses effective for neuropathic pain are usually lower than doses needed for depression. Amitriptyline has been most extensively studied. It blocks reuptake of serotonin and norepinephrine and appears to also block the NMDA receptor.[40] Amitriptyline is the most anti-cholinergic of the tricyclics. This fact can be used to advantage if patients have trouble sleeping at night. Often, however, the anti-cholinergic effects of dry mouth, sedation, constipation, and urinary retention are obstacles to use. Desipramine and nortriptyline have also been demonstrated to be effective for neuropathic pain and have much less anti-cholinergic activity.[41] All these agents are usually started at 10 mg orally at bedtime and titrated up to about 100 mg per day limited by effect or side effect. It typically takes 1-2 weeks to titrate up to an effective dose to determine if the therapy is working. Newer atypical anti-depressants (such as venlafaxine) show some evidence of

efficacy but they have not been well studied.[42] Studies have shown selective serotonin reuptake inhibitors (SSRIs) to be much less effective.

NMDA-receptor antagonists

The N-methyl-D-aspartate (NMDA) receptor may be involved in the spinal neural circuitry that leads to a neuropathic pain state resistant to high dose opioids. Clinically available NMDA-receptor antagonists include dextromethorphan, ketamine, and methadone. Clinical studies with dextromethorphan and ketamine have shown some mild pain effects, but have been significantly limited by dose-related side effects.[43] Methadone, however, is inexpensive and well tolerated. It exists as a racemic mix of levo and dextro isomers. The levo-form binds at opioid receptors, while both forms can block the NMDA receptor. As previously discussed, the equianalgesic dose of methadone varies dependent upon how much oral morphine equivalent a patient takes. It is hypothesized that by being both an opioid receptor agonist and an NMDA-receptor antagonist, methadone is much more potent than expected. Thus, methadone can be an extremely effective second-line opioid for neuropathic pain."

Local anesthetics

Local anesthetics that are non-selective inhibitors of sodium channels have also been utilized to treat neuropathic pain. Parenteral lidocaine has been studied and in general has been found to have efficacy in diabetic neuropathy, trigeminal neuralgia, and other neuropathic pain syndromes.[44] Typically effective serum levels range from 2-5 mg/liter. However, there is little data in the end of life population. Oral anesthetics/antiarrhythmics such as mexiletine have also been used with success in neuropathic pain. Monitoring for cardiac toxicity is necessary. Topical lidocaine patches have been approved for use in post-herpetic neuralgia.[45] Research has identified many subtypes of sodium channels. In the future, it may be possible to block a specific subset involved in mediating pain transmission.

Alpha-2-adrenergic agonists

Alpha-2-adrenergic agonists such as clonidine can also be effective adjuvant analgesics for both nociceptive and neuropathic pain.[46] They act at the level of the spinal cord in two ways. First, they act in a mechanistically similar way to the opioids. They act on the same neurons in the cord and lead to the same intracellular events but act through a different receptor.[47] Thus, it is likely that they can enhance the nociceptive effects of opioids. Second, researchers believe alpha-2-adrenergic agonists also decrease sympathetic outflow that is involved with neuropathic pain.[48] Clonidine can be given systemically or delivered intraspinally. Systemic delivery may be limited by the side effects of lethargy, dry mouth, and hypotension.

Corticosteroids

Corticosteroids are potent anti-inflammatory agents that are useful in both nociceptive and neuropathic pain. Reducing inflammation and peri-tumor edema can be important in relieving pressure on a nerve or the spinal cord, decreasing intracranial pressure from a brain tumor, or decreasing obstruction of a hollow viscus. At the end of life, dexamethasone is considered the corticosteroid of choice because of its minimal mineralocorticoid effects and thus its decreased tendency for salt and fluid retention.[49,50] Corticosteroids may also enhance pain control through the creation of a sense of euphoria. Most of the complications of steroid use are long-term sequelae and are not a concern at the end of life. However, steroid psychosis is occasionally a problem that may require either cessation of the drug or treatment with neuroleptics.[51] Dexamethasone has a long half-life and need only be dosed once a day. Typical doses range from 4 mg per day up to 100 mg intravenous bolus used for spinal cord compression.[52]

Bone pain

Bone pain is a frequently occurring problem that may be both constant at rest and much worse with movement. It is frequently the result of mechanical changes due to metastases, compression or pathologic fracture, etc. Prostaglandins produced by concurrent inflammation and/or metastases may increase bone pain severity. Cord compression should always be considered when there is significant back pain in the patient with metastatic cancer.

Bone pain is associated with inflammation. NSAIDs and/or corticosteroids are important components of the treatment of this pain syndrome. However, the treatment of choice for an isolated bone lesion is radiation therapy. At the end of life, when duration of effect is less important than efficacy and convenience, it can be delivered in a single fraction and promote improved pain within 1-2 weeks. When bony lesions are more diffuse or when they recur in a previously irradiated field, the bisphosphonates can play an important role. Osteoclasts are activated in bony metastasis. Bisphosphonates, like pamidronate, inhibit osteoclast activity, thus stabilizing bone and through an unknown mechanism can also relieve bone pain. It is effective for both lytic and sclerotic bone lesions.[53] Typical dosing of pamidronate is 90 mg intravenously over 2 hours every month. Radiopharmaceuticals such as strontium-89 are also available to treat diffuse lesions. They are typically more effective for sclerotic lesions but have also been shown to be effective in lytic lesions.[54]

Pain from bowel obstruction

Mechanical bowel obstruction, due to internal blockage from constipation or external compression by tumor or scars, can lead to significant abdominal pain as the bowel wall is stretched or inflamed. The pain is frequently described as constant, sharp, and cramping. It may be associated with considerable bloating, distention, gas, or even nausea/vomiting. Relief of constipation (see EPEC-O Module 3f: Symptoms -

Constipation) or surgical removal or bypass of external blockages may be definitive; in some patients, the obstruction will be irreversible.

Most patients will find the abdominal pain associated with bowel obstruction to be distressing. While some people will find opioids sufficient to manage this pain, many will need adjuvant medications to effectively relieve their discomfort. Corticosteroids or NSAIDs may be helpful. Anticholinergic medications (eg, scopolamine) or octreotide will reduce the volume of fluid entering the intestine, thus relieving the bowel wall stretch and the pain. Early consultation with a pain management expert can reduce patient distress even when awaiting definitive intervention.

Topical analgesia

Even simple procedures such as venipuncture may be painful. Topical anesthetic creams should always be considered. If trained, patients can always apply these analgesics in advance of office visits.

Open wounds may also be a source of considerable pain, particularly during dressing changes or debridement. If incident pain is significant, consider topical analgesics such as 10% lidocaine endotracheal spray or nitrous oxide puffers.

Adverse effects

Opioids have many possible adverse effects; some are common, and some are not.[55,56,57] If unmanaged, they may be a reason for non-adherence.[58] Addiction (psychological dependence), tolerance, and physical dependence are not considered among the adverse effects. The ethical considerations of 'double effect' and unintended consequences of opioids and other medications are discussed in EPEC-O Module 3: Symptoms.

Opioid allergy

Many people believe that opioid-induced nausea/vomiting, constipation, drowsiness, or even confusion is an allergic reaction. However, these are not allergic reactions; they are adverse effects. While one or more may present on initial dosing, adverse effects can be easily managed and patients generally develop pharmacologic tolerance to all but constipation within a relatively brief period.

Anaphylactic or true allergic reactions to opioids are rare. Urticaria and bronchospasm could be direct opioid effects or signs of allergy. Sudden onset of breathlessness or other signs of anaphylaxis should be taken very seriously, and the offending opioid replaced with another from a different class.

Urticaria, pruritus

In some patients, opioids produce urticaria or pruritus. These effects are the result of mast cell destabilization by the opioid and subsequent histamine release. Usually the rash and

pruritus can be managed by routine administration of long-acting, nonsedating antihistamines while opioid dosing continues (eg, fexofenadine, 60 mg PO bid; diphenhydramine, loratadine, or doxepin, 10–30 mg PO nightly).

Constipation

Constipation secondary to opioid administration is almost universal. It is primarily the result of opioid effects on the central nervous system, spinal cord, and myenteric plexus of gut that, in turn, reduce gut motor activity and increase stool transit time. The colon has more time to desiccate its contents, leaving large hard stools that are difficult to pass. Other factors, such as dehydration, poor food intake, other medications, etc, may make the problem worse.

Tolerance to constipation may develop very slowly, if at all.[32,33] It requires anticipatory and ongoing management. Dietary interventions alone (eg, increase fluid and fiber) are often insufficient. Bulk-forming agents (eg, psyllium) require substantial fluid intake and are not recommended for those with advanced disease and poor mobility.

To counteract the slowing effect of opioids, start by prescribing a routine stimulant laxative (eg, senna, bisacodyl, glycerine, casanthranol, etc.) and escalate the dose to effect. While stool softeners (eg, docusate sodium) are not usually effective by themselves, combination stimulant/softeners (eg, senna + docusate sodium or calcium) can be useful. Prokinetic agents (eg, metoclopramide, cisapride, etc.) may also significantly counteract the opioid effect. If constipation persists, some patients will benefit from the addition of an osmotic agent, such as milk of magnesia, lactulose, or sorbitol, to increase the stool's moisture content. If the constipation proves to be refractory to basic therapy, interventions that are more aggressive may be necessary (see EPEC-O Module 3: Symptoms).

Nausea/vomiting

Many patients starting opioids experience nausea with or without vomiting. It is easily anticipated and treated with antiemetics and usually disappears as tolerance develops within a few days. Young women seem to be most at risk. Opioid induced nausea may be related to stimulation of the chemoreceptor trigger zone, the vestibular apparatus, and to delayed gastric emptying. Nausea typically responds well to anti-emetics that target the chemoreceptor trigger zone such as anti-dopaminergic agents, target the vestibular apparatus such as antihistamines, and target gastric motility.

Dopamine-blocking agents (eg, prochlorperazine, 10 mg before opioid and q 6 h; haloperidol, 1 mg before opioid and q 6 h; metoclopramide, 10 mg before opioid and q 6 h) are most often effective. In refractory cases, a more aggressive approach or an alternative opioid may become necessary (see EPEC-O Module 3: Symptoms).

Sedation

Patients sometimes complain of feeling sedated or mentally clouded immediately after beginning an opioid analgesic. Care must be taken to distinguish true sedation (inability to fully wake up) from exhaustion due to previous sleep deprivation with the unrelieved pain (sleeps a lot, but is able to wake fully between sleeps). Opioid-induced sedation usually disappears over a few days as tolerance develops. Most patients also catch up on their lost sleep over a week or two.

For patients with very advanced disease, mental clouding and excessive somnolence are often issues, particularly when patients have multiple concomitant medical conditions, medications, and declining function, even in the absence of opioid analgesics. Pain may, in fact, be the primary stimulant keeping them alert. Once pain is managed, the patient's 'natural' level of sedation may become apparent.

If sedation occurs, encourage patients and families to clearly articulate their goals (see EPEC-O Module 9: Negotiating Goals of Care) and develop a pain management plan that balances alertness and pain control to suit the individual. Some patients may prefer to be sleepy and comfortable, rather than alert and in pain.

If undesired sedation persists, a different opioid or an alternate route of administration may provide relief. Also, consider the use of a psychostimulant (eg, methylphenidate, 5 mg q am and q noon and titrate), particularly if the opioid is providing effective analgesia.[31]

Delirium

The onset of confusion, bad dreams, hallucinations, restlessness, agitation, myoclonic jerks, a significantly depressed level of consciousness, or seizures suggests delirium due to opioid excess. If opioid dosing guidelines are followed closely, delirium rarely occurs in patients who have normal renal clearance. However, one or more of these adverse effects may present gradually (eg, in the patient who is not passing much urine and is accumulating opioid due to decreased intake or dehydration) or rapidly (eg, in the patient who is developing sepsis) (see EPEC-O Module 3: Symptoms).

Respiratory depression

Many physicians have an exaggerated view of the risk of respiratory depression when using opioids to relieve pain.[31] The inappropriate application of animal and human models from acute pain research is in part responsible for this fear.

Pain is a potent stimulus to breathe, and pharmacologic tolerance to respiratory depression develops quickly. Opioid effects are quite different from those experienced by a patient who is not in pain and receives similar doses. As doses increase, respiratory depression does not occur suddenly in the absence of overdose. Somnolence always precedes respiratory depression. Adequate ongoing assessment and appropriate titration

of opioids based on pharmacologic principles will prevent misadventures. Patient-controlled analgesia with an appropriate dosing interval (10–15 minutes if IV, 30 minutes if SC) can be used safely, because the patient who takes too many extra doses of opioid will fall asleep and stop pushing the button before respiratory depression occurs.

If delirium due to opioid excess does occur, but respirations are not compromised (> 6/min), the routine opioids may be stopped and the patient appropriately hydrated or sepsis managed until the adverse effects abate.

 If respirations are compromised (< 6/min), naloxone may be necessary if it is the goal of care to keep the patient alert while treating the underlying cause. Dilute 0.4 mg of naloxone to 10 ml with sterile water. Administer 0.1 to 0.2 mg IV q 1 to 2 min until the patient is alert. As the effective plasma half-life is short (10 to 15 minutes) because of naloxone's high affinity for lipids, monitor the patient closely every few minutes for recurrent drowsiness. If drowsiness recurs, repeat dosing as required until the patient is no longer compromised.

Interventional pain management for refractory pain

About 14% of cancer pain patients suffer severe unrelieved pain even when treated with opioids, adjuvant drugs, and other accepted therapies.[58] In addition, pain drugs relieve pain but often have side effects severe enough to prevent relief.[59] Interventional pain management can help this subgroup of patients with intraspinal therapy, splanchnic nerve block, and local nerve blocks.[60] Interventional pain management works quickly if it is going to work; unlike chemotherapy, the patient will either say, "Geez, I wish I had done that months ago!" or note no difference.

Prognosis

Pain is associated with a poor prognosis, but it is not clear if pain itself or the disease causing the pain is the root issue. Pain itself dampens immune system function, as do therapeutic doses of morphine.[61,62,63] In patients with pain due to pancreas cancer, relief of pain by an alcohol celiac plexus block vs. placebo saline block at the time of pancreaticoduodenectomy was associated with a markedly improved median survival of greater than 6 months.[64] Relief of pain and drug side effects was associated with a near doubling of median survival in patients with refractory pain.[60]

Intraspinal therapy

The two most common ways of giving intraspinal therapy are by epidural or intrathecal treatment.[65,66,67,68,69,70] The reduced systemic exposure to opioids can help relieve refractory effects of narcotics such as constipation, nausea, and sedation. Epidural catheters are commonly used to produce mostly a local effect in the area where the catheter instills drugs for relatively short periods of time (days to weeks). Intrathecal

catheters instill drugs directly into the spinal canal and can be used to give both local and systemic pain relief for periods of months to years.

Epidural therapy provides pain relief in the small number of patients in whom it is appropriate.[71,72] However, complications such as dislodged or broken catheters, pain on injection, bruising, bleeding, and infection occurred in half.

Intrathecal therapy provides pain relief by instilling small doses of morphine or other drugs directly to the cerebrospinal fluid.[73]

An implanted pump is used for long term administration. Prior to implantation of a pump, all patients receive a screening trial of intraspinal morphine to determine response. About 95% of patients who have a 'trial' have successful treatment of pain and can go on to an implanted system. The implanted system consists of a small battery powered pump that is implanted in the abdomen connected to a small catheter tunneled to the site of spinal entry, usually the L1-2 interspace. Patients with implanted pumps may continue to use systemic medications to manage breakthrough pain. There two types of pumps: a programmable pump that allows the rate of infusion to be changed just like changing the rate on a pacemaker, and a non programmable pump that requires changing the concentration of the infusate.

Relative contraindications to intraspinal therapy include active infection, coagulopathy or heparin, or spinal cord obstruction that would prevent diffusion of the drugs. Patients with a short time to live are best served by catheters connected to external re-useable pumps; those with 3 or more months to live are candidates for implantable pumps.

Celiac plexus blocks

Celiac plexus block (CPB) is used to treat the severe, boring, progressive pain of upper abdominal cancers (most commonly pancreas, stomach, liver, gallbladder, and colon) that fails to respond to conventional treatment. A review reported a satisfactory response in 87% of pancreas cancer patients, with the expected relief of pain but also relief of anorexia and constipation.[74] About 10-20% of patients will have complete resolution of their pain and for many patients the pain relief lasts until death.[75,76]

The celiac plexus partly innervates all the abdominal structures including the diaphragm, stomach, adrenal glands, liver, spleen, intestines, and even gonads. CPB is the injection of a local anesthetic into the celiac plexus in front of the L1 vertebra, which if successful, can be followed by injection of a neurolytic substance such as alcohol or phenol. CPB can be done percutaneously with CAT or fluoroscopic guidance, or intraoperatively. Serious complications are rare with experienced hands.[77,78] More common and predictable complications such as hypotension and postural hypotension, require careful post-op observation, and transient post block diarrhea (due to sympathetic block) which remits in several days.

CPB should be considered early in the course of the disease – not done as a last ditch effort with 10 days to live. The data showing a high success rate with CPB, low complication rate, ability to relieve upper abdominal pain without need for high dose opioids, and improvement in overall survival support this claim.

Other nerve stimulations or ablations

Consider invasive techniques if their purpose is to provide better function. Some procedures that have been shown to be useful in highly selected patients include at least the following: stimulation of the spinal cord, cortical brain, or brain stem; and temporary nerve blocks followed by radiofrequency or cryosurgical ablation. In each instance, large scale randomized clinical trials have not been carried out due to the infrequency (or lack of recognition) of refractory pain or infrequency of use (due to lack of expertise or appropriate consultation), but there is substantial evidence of effectiveness. In all cases, there is the opportunity to test the procedure first to see if effective, and then do a more permanent maneuver.[79,80,81]

Non-pharmacologic pain management techniques

While pharmacologic approaches may be the mainstay of pain management, physicians should consider all available therapies as they develop an individual's plan of care. Many patients have realized significant relief through neurostimulatory techniques, including TENS (transcutaneous electrical nerve stimulation) and acupuncture; physical therapy including therapeutic exercises, heat, and cold; psychological approaches including cognitive therapies (relaxation, imagery, hypnosis), biofeedback, behavior therapy, and psychotherapy; art or music therapy; massage, and body work; etc. Members of the interdisciplinary team, who may be more familiar with non-pharmacologic interventions, can frequently assist the physician to identify and refer patients appropriately.

Barriers

Today, pain management remains inadequate in spite of the fact that we have possessed information discussed in this module for more than 20 years. While this inadequacy may reflect inadequate knowledge, it also reflects barriers to pain relief that are pervasive and (in some cases) institutional. To become effective, we need to overcome real or perceived barriers, including beliefs by physicians and other professionals that pain management is not important; poor assessment techniques; inadequate dissemination of the available knowledge; unfounded fear of addiction, tolerance, and adverse effects; and inappropriate regulatory oversight. To be effective, individual care plans must encourage patients to report their pain freely and take into account each patient's willingness to take medication, or not. In addition to adequate knowledge, health care systems and institutions may need to change in order to facilitate the implementation of the knowledge.

Summary

Pain management is key to achieving the goal of relief of suffering. Although pain control alone is not sufficient to relieve suffering, there can be little progress in the other spheres of experience if pain is uncontrolled. If we simply apply the knowledge we have, we will adequately relieve pain in the majority patients. Careful assessment and appropriate use of opioids as outlined in the WHO 3-step ladder approach will go a long way toward improving the quality of our patients' lives.

Key take-home points

Assessment

1. Characterize the nature of the pain (nociceptive, neuropathic, psychological/social/spiritual). Try to establish the cause of the pain. Understand the personal context in which the pain is experienced.

Management

2. There is no reason to delay the use of analgesics while diagnosing and treating the underlying cause of the pain.

3. There is no ethical or scientific basis for the use of placebos to assess or treat pain.

WHO analgesic ladder

4. A 3-step model to guide analgesic choice depending on the severity of the patient's pain.

5. The non-opioid analgesics that characterize step 1 of the WHO ladder (acetaminophen, NSAIDs) all have a ceiling effect to their analgesia. Start with moderate to maximal doses to achieve optimal efficacy quickly.

6. The step 1 analgesics have the greatest risk of severe adverse effects. Anticipate and monitor for them carefully.

7. Step 2 and 3 opioid analgesics (eg, codeine, hydrocodone, hydromorphone, morphine, oxycodone) follow first-order kinetics. They reach their peak effect and plasma concentration (Cmax) approximately 60 to 90 minutes after oral or rectal administration, 30 minutes after subcutaneous or intramuscular injection, and 6 minutes after intravenous injection.

Opioid dosing

8. In general, the oral route is the least invasive, most convenient route for administering opioids on a routine basis.

9. If the pain is continuous, or nearly so, start with an appropriate dose of an immediate-release opioid routinely q 4 h around the clock.

10. If pain remains uncontrolled after 24 hours, increase the routine dose by an amount at least equal to the total dose of rescue medication used during the previous 24 hours, or by 25-50% for mild to moderate pain, 50-100% for severe to uncontrolled pain.

11. Once the continuous pain is controlled, switch to an extended-release preparation to simplify routine dosing and increase the chance of patient adherence.

Breakthrough pain

12. Transitory flares of pain, called 'breakthrough pain,' can be expected both at rest and during movement.

13. For each breakthrough dose, offer 5-15% of the total 24-hour dose of opioid at a frequency equal to Cmax for the chosen route of administration.

$$PO/PR \approx \quad q\ 1\ h\ PRN$$
$$SC/IM \approx \quad q\ 30\ min$$
$$IV \quad\ \approx \quad q\ 10\text{-}15\ min$$

Clearance concerns

14. As some morphine metabolites remain active until they are excreted in the urine, adjust routine dosing for decreased renal clearance when oliguria or anuria is present (eg, dehydration, renal failure, dying patient).

Opioids to avoid

15. Meperidine is not recommended for routine dosing because of the high risks of adverse effects from accumulation of the metabolite normeperidine.

16. Propoxyphene is typically administered at doses that produce relatively little analgesia and is not recommended as a routine analgesic.

17. The mixed opioid agonist-antagonists, such as pentazocine, butorphanol, nalbuphine, and dezocine, should not be used in the patient already taking a pure agonist opioid as there is a high risk they will precipitate withdrawal.

Addiction, tolerance, physical dependence

18. The perception that the administration of opioids and analgesics for pain management causes addiction is a prevalent myth that inhibits adequate pain control.

19. Addiction is a complex phenomenon. Its hallmark is psychological dependence on drugs and a behavioral syndrome characterized by compulsive drug use and continued use despite harm. Distinguish between true addiction, pseudoaddiction

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caused by undertreatment of pain, behavioral/family/psychological dysfunction, and drug diversion with criminal intent.

20. Pharmacologic tolerance is defined as the reduced effectiveness of a given dose of medication over time. Clinical importance is rare. When increasing doses are required, suspect worsening disease rather than pharmacologic tolerance.

21. Physical dependence is the result of neurophysiologic changes that occur in the presence of exogenous opioids. Withholding opioids after physical dependence develops results in transient withdrawal symptoms. Physical dependence is not the same as addiction.

Alternate routes and changing opioids

22. All opioids available for parenteral use may be administered subcutaneously without the discomfort associated with searching for an IV site, the risk of serious infection, or the discomfort of intramuscular (IM) injection.

23. Intramuscular injections are not recommended.

24. When changing routes of administration, or switching between opioids, an equianalgesic table is a useful guide for initial dose selection.

25. Incomplete cross-tolerance is likely caused by subtle differences in the molecular structure of each opioid and the way each interacts with the patient's opioid receptors. Consequently, when switching opioids, there may be differences between published equianalgesic doses of difference opioids and the effective ratio for a given patient. Start with 50-75% of the published equianalgesic dose of the new opioid if pain is otherwise well controlled.

Neuropathic pain

26. Opioids may contribute significantly to the management of neuropathic pain.

27. For burning, tingling pain with or without numbness, tricyclic antidepressants or gabapentin are the most widely used adjuvant medications.

28. Desipramine has minimal anticholinergic adverse effects and is the tricyclic antidepressant of choice, particularly in elderly and frail patients. Start with 10 to 25 mg orally at bedtime and escalate every 4 to 7 days. This may be effective in only a few days.

29. For episodic shooting, stabbing, electrical pain, the anticonvulsants gabapentin, carbamazepine, and valproic acid are the most widely used adjuvant medications. Start with low doses and escalate after a steady-state equilibrium has been reached (varies by medication).

Bone pain

30. Opioids remain the mainstay of bone pain management. NSAIDs and steroids may be effective adjuvants.

Steroids

31. Corticosteroids are frequently helpful and commonly used in advanced illness. Dexamethasone, with its long half-life (>36 hours) and minimal mineralocorticoid effect, is the adjuvant steroid of choice. It can be administered once a day.

Adverse effects of opioids

32. Addiction (psychological dependence), tolerance, and physical dependence are not considered adverse effects of opioid analgesics.

33. Concerns about the double effect of opioids are overrated. The term is frequently misused. If opioid dosing guidelines are followed, the risk of a secondary, potentially severe unintended consequence is minimal. Severe and predictable adverse effects such as death are almost unknown.

34. Many people believe that opioid-induced nausea/vomiting, constipation, drowsiness, or even confusion are allergic reactions. They are in fact adverse effects, not allergic reactions.

35. Urticaria and pruritus are usually the result of mast cell destabilization by opioids that lead to histamine release. This can be managed by the routine administration of long-acting nonsedating antihistamines or mast cell stabilizers.

36. Adverse effects of opioids can be managed. Patients generally develop pharmacologic tolerance to all but constipation within a relatively brief period.

37. Constipation secondary to opioid administration is almost universal. When starting opioid therapy, prevent it by prescribing a routine stimulant laxative and escalate the dose to effect.

38. Many patients starting opioids (up to 30%) experience nausea with or without vomiting. Tolerance develops. Treat with antiemetics or change to a different opioid.

39. Opioid induced sedation usually disappears over a few days as tolerance develops. For patients with far-advanced disease near the end-of-life, pain may, in fact, be the primary stimulant keeping them alert. Once pain is managed, the patient's "natural" level of sedation may become apparent. Encourage patients and families to clearly

articulate their goals and priorities in order to develop a pain management plan that balances alertness and pain control.

40. The onset of confusion, bad dreams, hallucinations, restlessness, agitation, myoclonic jerks, a significantly depressed level of consciousness, or seizures suggests delirium caused by opioid excess.

41. Physicians often have an inordinate fear of respiratory depression caused by opioids. Pain is a potent stimulus to breathe. Pharmacologic tolerance to respiratory depression develops quickly. Somnolence always precedes respiratory depression.

Non-pharmacologic approaches

42. Non-pharmacologic approaches to pain management may have a significant adjunct effect on pain management.

Barriers

43. There are many unnecessary and remediable barriers to pain management.

Pearls

1. Believe the patient.

2. Be the physician you would want if you were in pain.

3. Dehydration may present as confusion caused by opioid accumulation.

4. Opioids do not cause the psychological dependence involved in addiction.

5. Doxepin is a potent H_1 histamine antagonist.

6. Teach the patient and family about potential adverse effects. Unexpected adverse effects may cause the patient to refuse any further opioid therapy.

7. Constipation is easier to prevent than treat.

8. Psychostimulants may be useful adjuncts to counteract sedation.

9. Dehydration may present as delirium caused by opioid accumulation.

10. Sepsis may present as delirium caused by effective opioid excess.

Pitfalls

1. Using extended-release preparations for initial dose titration.

2. Mixing opioids.

3. Detergent stool softeners alone (eg, docusate) at conventional doses do not counteract the constipation effect of opioids.

4. Failing to distinguish sleepiness caused by exhaustion once pain is relieved from sedation caused by overmedication.

5. Mismanaging terminal delirium with opioids, which may make it worse.

6. Unfounded fear of respiratory depression and lack of skill with opioid dosing leading to significant unnecessary pain, loss of function, and suffering.

Problem solving

The following cases illustrate common issues in cancer pain management. Answers can be found at the end of the Appendix.

Case 1

Mrs. D. is a 45-year-old attorney who has breast cancer metastatic to bone. She is comfortable on a continuous infusion of morphine at 6 mg/h SC. Your goal is to change to oral medications before discharging her home. What should your prescription be?

Case 2

Mr. T. is a 73-year-old man with lung cancer, a malignant pleural effusion, and chronic chest pain. He has undergone therapeutic thoracentesis and pleurodesis. He is currently receiving meperidine, 75 mg IM q 6 h, for pain. You want to change to oral morphine. Without adjusting for cross-tolerance, what dose and schedule would you choose?

Case 3

Ms. M. is a 41-year-old teacher who has ovarian cancer with ascites and has been taking 2 tablets of acetaminophen/hydrocodone (500 mg/5 mg) every 4 hours and 1 tablet of acetaminophen/oxycodone (325 mg/5 mg) every 6 hours for pain relief. Morphine makes her nauseated. You are concerned about acetaminophen toxicity and want to change to an alternative oral approach. Without adjusting for partial cross-tolerance, what dose of hydromorphone would you choose?

Case 4

Mrs. A. is hospitalized and receiving adequate pain control with meperidine, 120 mg intramuscularly every 3 hours. She is now able to take nutrition and medications by mouth. Correcting 25% for incomplete cross-tolerance, what dose and schedule of oral hydromorphone would you prescribe to provide her with an approximately equal amount of analgesia?

    a. 2 mg PO q 4 h

    b. 4 mg PO q 4 h

    c. 8 mg PO q 4 h

    d. 12 mg PO q 4 h

Case 5

Mr. B. has been taking 3 capsules containing oxycodone (5 mg per capsule) and aceta-minophen every 3 hours at home for relief of bone pain from metastatic lung cancer. He is now admitted to the hospital with a chemotherapy-induced aplasia. You do not want him taking an antipyretic (acetaminophen). Without correcting for partial cross-tolerance, how much oral morphine elixir would you prescribe to provide analgesia similar to that which he received from the oxycodone?

    a. 5 mg PO q 4 h

    b. 10 mg PO q 4 h

    c. 20 mg PO q 4 h

    d. 30 mg PO q 4 h

Case 6

Mrs. C. has been taking codeine, 60 mg by mouth every 4 hours, and methadone, 40 mg orally every 6 hours, to adequately control abdominal pain from bulky retroperitoneal metastases. She is now admitted with a chemotherapy-induced stomatitis. Your attending physician suggests that you place her on a constant infusion of intravenous morphine. Without adjusting for partial cross-tolerance, what hourly rate of intravenous morphine will you choose to continue to keep her pain well controlled?

    a. 1 mg/h

    b. 2 mg/h

    c. 4 mg/h

    d. 8 mg/h

Case 7

John is a 40-year-old accountant with AIDS (acquired immunodeficiency syndrome). His most recent T4 count is 34. He has noted a burning pain in his hands and feet for the past

2 years. It initially appeared after he began zalcitabine (ddC) in addition to zidovudine (AZT) and resolved when the ddC was discontinued. However, during the past 6 months the pain has returned. It is severe, keeps him awake at night, and is associated with numbness of his feet. He has trouble buttoning his shirt. How would you manage John's pain?

[Answers for Cases 7-9 are indicated in the appendix of this module.]

Case 8

Sarah is a 73-year-old attorney who has breast cancer with metastases to bone. She was treated with three cycles of AC (adriamycin, cyclophosphamide) without response. Pain persists, even after 2 months of tamoxifen. How would you manage Sarah's pain?

Case 9

David is a 67-year-old farmer with colon cancer metastatic to liver. He has complained of increasing right upper quadrant pain. Examination reveals a tender liver, but no shifting dullness to percussion of his abdomen. How would you manage David's pain?

Case 10

George is a 37-year-old otherwise healthy engineer with hepatoma who has excruciating hip and back pain due to bone metastases, treated with radiation. He was barely able to walk due to excruciating pain despite sustained release oxycodone 80 mg every 8 hours, gabapentin 800 mg every 8 hours, and acetaminophen/oxycodone for breakthrough pain. He rated his pain as 10/10 at rest and 12/10 with motion, and had dose-limiting fatigue, drowsiness, dulled thinking, and constipation despite appropriate remedies of methylphenidate, opioid rotation, treatment of constipation, etc. How would you manage his pain?

Appendix

Morphine: initial dosing for constant pain

A. For a patient with significant previous opioid exposure, calculate the starting dose for an immediate-release opioid using the equianalgesic table (to begin the new opioid you will cut back on this dose as appropriate) and dose q 4 h, or

B. For a patient who is relatively opioid naive and in significant pain, start dosing with 10 to 30 mg of immediate-release oral morphine liquid concentrate or tablet q 4 h, or

C. For a patient with stable pain that is not severe, start extended-release oral morphine at a dose of 15 or 30 mg twice daily or 30 to 60 mg once daily (depending on formulation).

Then, prescribe a 'breakthrough' or rescue dose that is 5-15% of the total dose in use every 24 hours and offer it q 1 h PO PRN. Ask the patient and family to record in a diary all medication taken.

To convert to an extended-release preparation, calculate the total morphine dose required to achieve comfort during a 24-hour period. Either divide by 2 to get the q 12 h dose of extended-release morphine to prescribe routinely, or give the total dose once daily (depending on the product).

Always prescribe a breakthrough dose of immediate-release morphine using liquid concentrate or tablet. Offer 5-15% of the 24-hour dose q 1 h PO PRN.

Monitor closely and titrate as needed.

Morphine: increasing the dose

1. If a patient requires more than 2 to 4 breakthrough doses in a 24-hour period on a routine basis, consider increasing the dose of the extended-release preparation.

2. Determine the total amount of morphine used (routine + breakthrough) and administer the total in divided doses q 12 h or q 24 h (depending on the product).

3. Recalculate the breakthrough so that it is always 5-15% of the total daily dose and offer it q 1 h PO.

NB: In the patient with cancer, the most common reason for an increased dose is worsened pathology, not pharmacologic tolerance.

Answers to problems

For all of these cases, remember non-pharmacologic approaches as a possibility and remember to consider possible barriers to good use of pain interventions.

Case 1

Mrs. D. is a 45-year-old attorney who has breast cancer metastatic to bone. She is comfortable on a continuous infusion of morphine at 6 mg/h SC. Your goal is to change to oral medications before discharging her home. What should your prescription be?

Answer

1. Figure out total daily dose of IV morphine

   6 mg/h x 24 hours = 144 mg/d IV morphine

2. Set up a ratio using values from the table

   144 mg/d IV morphine = 1 mg IV morphine

   X mg/d oral morphine = 3 mg oral morphine

3. Solve for X

$X = 442$ mg/d oral morphine

4. Divide by 2 for bid formulation of extended-release morphine, or divide by 6 for immediate-release morphine administered every 4 hours.

   Sig: 200 mg extended-release morphine PO bid, or 70 mg immediate-release morphine PO q 4 h RTC

5. Also prescribe a breakthrough dose of 5% to 15% of total daily dose

   Sig: 20–60 mg immediate-release morphine PO q 1 h PRN

6. Do not forget a stimulant laxative!

Case 2

Mr. T. is a 73-year-old man with lung cancer, a malignant pleural effusion, and chronic chest pain. He has undergone therapeutic thoracentesis and pleurodesis. He is currently receiving meperidine, 75 mg IM q 6 h, for pain. You want to change to oral morphine. Without adjusting for cross-tolerance, what dose and schedule would you choose?

Answer

1. Figure out total daily dose

   4 x 75 mg IM meperidine = 300 mg/d IM meperidine

2. Set up ratio from the table

300 mg/d IM meperidine	=	50 mg IM meperidine
X mg/d PO morphine	=	15 mg PO morphine

3. Solve for X

   $X = 90$ mg/d PO morphine

4. Decide on schedule and formulation

   Sig: sustained-release morphine, 45 mg PO bid

   Remember breakthrough dose

   Sig: 5–15 mg PO immediate-release morphine q 1 h PRN

5. Remember the stimulant laxative

Case 3

Ms. M. is a 41-year-old teacher who has ovarian cancer with ascites and has been taking 2 tablets of acetaminophen/hydrocodone (500 mg/5 mg) every 4 hours and 1 tablet of acetaminophen/oxycodone (325 mg/5 mg) every 6 hours for pain relief. Morphine makes her nauseated. You are concerned about acetaminophen toxicity and want to change to an

alternative oral approach. Without adjusting for partial cross-tolerance, what dose of hydromorphone would you choose?

Answer

1. Figure out total daily dose of each opioid

    2 tablets x 5 mg hydrocodone/tablet x 6 = 60 mg/d hydrocodone

    1 tablet x 5 mg oxycodone/tablet x 4 = 20 mg/d oxycodone

2. Set up ratios from the table

    60 mg/d oral hydrocodone = 15 mg oral hydrocodone

    X mg/d oral hydromorphone = 4 mg oral hydromorphone

    20 mg/d oral oxycodone = 10 mg oral oxycodone

    X mg/d oral hydromorphone = 4 mg oral hydromorphone

3. Solve for X in each case

    X = 16 mg/d PO hydromorphone

    X = 8 mg/d oral hydromorphone

4. Add them together for a total of 24 mg/d oral hydromorphone

5. Decide on schedule

    Sig: Hydromorphone, 4 mg PO q 4 h RTC

6. Don't forget breakthrough

    Sig: Hydromorphone, 1–2 mg PO q 1 h PRN

7. Do not forget a stimulant laxative

Case 4

Mrs. A. is hospitalized and receiving adequate pain control with meperidine, 120 mg intramuscularly every 3 hours. She is now able to take nutrition and medications by mouth. Correcting 25% for incomplete cross-tolerance, what dose and schedule of oral hydromorphone would you prescribe to provide her with an approximately equal amount of analgesia?

Answer

   c. 8 mg PO q 4 h

Calculating the answer

1. Figure out total daily dose of each opioid

120 mg x 8 = 960 mg/d IM meperidine

2. Set up ratios from the table

$$\frac{960 \text{ mg/d IM meperidine}}{X \text{ mg/d oral hydromorphone}} = \frac{50 \text{ mg IM meperidine}}{3 \text{ mg oral hydromorphone}}$$

3. Solve for X

X = 57.6 mg/d PO hydromorphone

4. Decide on schedule (divide by 6 for q 4h dosing)

10 mg PO q 4 h

5. Adjust 25% for incomplete cross-tolerance

Sig: Hydromorphone, 8 mg PO q 4 h

Case 5

Mr. B. has been taking 3 capsules containing oxycodone (5 mg per capsule) and aceta-minophen every 3 hours at home for relief of bone pain from metastatic lung cancer. He is now admitted to the hospital with a chemotherapy-induced aplasia. You do not want him taking an antipyretic (acetaminophen). Without correcting for partial cross-tolerance, how much oral morphine elixir would you prescribe to provide analgesia similar to that which he received from the oxycodone?

Answer

d. 30 mg PO q 4 h

Calculating the answer

1. Figure out total daily dose of opioid

3 tablets x 5 mg oxycodone/tablet x 8 = 120 mg/d oxycodone

2. Set up ratio from the table

$$\frac{120 \text{ mg/d oral oxycodone}}{X \text{ mg/d oral morphine}} = \frac{10 \text{ mg oral oxycodone}}{15 \text{ mg oral morphine}}$$

3. Solve for X

X = 180 mg/d oral morphine

4. Decide on schedule

Sig: Morphine, 30 mg PO q 4 h RTC

Case 6

Mrs. C. has been taking codeine, 60 mg by mouth every 4 hours, and methadone, 40 mg orally every 6 hours, to adequately control abdominal pain from bulky retroperitoneal metastases. She is now admitted with a chemotherapy-induced stomatitis. Your attending physician suggests that you place her on a constant infusion of intravenous morphine. Without adjusting for partial cross-tolerance, what hourly rate of intravenous morphine will you choose to continue to keep her pain well controlled?

Answer

c. 4 mg/h

Calculating the answer

1. Figure out total daily dose of each opioid

24 hour dose of Methadone = 4 x 40mg or 160 mg daily

24 hour dose of codeine is 60 mg x 6 or 360 mg daily.

2. Set up ratio from the table. Since the table for methadone only gives oral dose. Convert to oral, first

$$\frac{160 \text{ mg/d oral methadone}}{X \text{ mg/d oral morphine}} = \frac{1 \text{ oral methadone}}{3 \text{ mg oral morphine}}$$

X = 480 mg/d oral morphine

$$\frac{120 \text{ mg/d oral oxycodone}}{X \text{ mg/d oral morphine}} = \frac{10 \text{ mg oral oxycodone}}{15 \text{ mg oral morphine}}$$

X = 180 mg/d oral morphine

Total oral morphine equivalent is 660 mg/day of oral morphine

98 mg ÷ 24 h = **4 mg/h**

Case 7

John is a 40-year-old accountant with AIDS (acquired immunodeficiency syndrome). His most recent T4 count is 34. He has noted a burning pain in his hands and feet for the past 2 years. It initially appeared after he began zalcitabine (ddC) in addition to zidovudine (AZT) and resolved when the ddC was discontinued. However, the past 6 months the pain has returned. It is severe, keeps him awake at night, and is associated with numbness of his feet. He has trouble buttoning his shirt. How would you manage John's pain?

Answer

Consider opioids, tricyclic antidepressants, gabapentin, and other adjuvants for neuro-pathic pain.

Case 8

Sarah is a 73-year-old attorney who has breast cancer with metastases to bone. She was treated with three cycles of AC (adriamycin, cyclophosphamide) without response. Pain persists, even after 2 months of tamoxifen. How would you manage Sarah's pain?

Answer

Consider NSAIDs, steroids, and bisphosphonates as well as radiation.

Case 9

David is a 67-year-old farmer with colon cancer metastatic to liver. He has complained of increasing right upper quadrant pain. Examination reveals a tender liver, but no shifting dullness to percussion of his abdomen. How would you manage David's pain?

Answer

Consider opioid analgesics and steroids to decrease capsular stretch.

Case 10

George is a 37-year-old otherwise healthy engineer with hepatoma who has excruciating hip and back pain due to bone metastases, treated with radiation. He was barely able to walk due to excruciating pain despite sustained release oxycodone 80 mg every 8 hours, gabapentin 800 mg every 8 hours, and acetaminophen/oxycodone for breakthrough pain. He rated his pain as 10/10 at rest and 12/10 with motion, and had dose-limiting fatigue, drowsiness, dulled thinking, and constipation despite appropriate remedies of methylphenidate, opioid rotation, treatment of constipation, etc. How would you manage his pain?

Answer

Admit for a trial of epidural morphine. A catheter was placed at the L1-L2 interspace. Morphine 0.6 mg/hour was started. The dose of oxycodone was reduced by 50% to 40 mg every 8 hours, and Percocet was available for breakthrough pain. Within two hours of epidural placement, his pain VAS score was reduced from 10/10 at rest to 2/10, but movement increased the pain to 6/10. Morphine was increased to 1.0 mg/hour which reduced the pain to 1/10. Bupivicaine at 0.1% concentration, 5 ml/hour, was added. With the combination, his pain score was reduced to 0-2/10 and he was able to bear weight on the right leg for the first time in months. He had no sensory or motor changes with either

drug, and felt much less sedated. An implanted pump was placed to maintain the therapy. Oxycodone and gabapentin were tapered, then discontinued.

References

[1] Schweitzer A. *The Primeval Forest*. Baltimore: Johns Hopkins University Press; 1931:74. ISBN: 0-8018-6034-2. Full text

[2] Weiss SC, Emanuel LL, Fairclough DL, Emanuel EJ. Understanding the experience of pain in terminally ill patients. *Lancet*. 2001;357(9265):1311-1315. PMID: 11343734.

50% of 988 terminally ill patients reported pain. Of those patients experiencing moderate or severe pain, 29% wanted more therapy, 61% wanted therapy to remain the same, while 9% wanted less therapy or to stop their pain treatment altogether. Of these, 34% feared addiction, 31% were adverse to physical side effects (eg constipation), 33% averse to mental side effects (eg confusion) and 30% averse to additional pills or injections. Although the majority of patients had cancer, there was no association between disease and level of pain. The authors conclude the majority of patients experiencing pain are willing to tolerate their pain; they trade off experiencing pain for other goods. The experience of pain is constant across diseases.

[3] Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. *Qual Life Res*. 1994;3:183-189. PMID: 7920492.

Systematic assessment of prevalence eand characteristics of symptoms in 243 patients at Memorial Sloan-Kettering. Mean age 55.5 (range 23-86). 123 were inpatients. 40-80% experienced lack of energy, pain, feeling drowsy, dry mouth, insomnia or symptoms of psychological distress. The mean number of symptoms per patients was 11.5 + 6.0; inpatients had more symptoms than outpatients (13.5 vs 9.7) and those with Karnofsky performance score < 80 had more symptoms than those with a higher score (14.8 vs 9.2).

[4] Yaksh TL, Chaplan SR. Physiology and Pharmacology of neuropathic pain. In: Wallace MS, Dunn JS, Yaksh TL, guest editors, Benumof JL, consulting editor. Anesthesiology Clinics of North America (Pain: Nociceptive and Neuropathic Mechanisms with Clinical Correlates). Philadelphia:W.B. Saunders Company, 1997:335-352.

Injury to nervous tissues gives rise to clinical pain syndromes.

[5] Sorkin LS. Basic pharmacology and physiology of acute pain processing. In: Wallace MS, Dunn JS, Yaksh TL, guest editors, Benumof JL, consulting editor. Anesthesiology *Clinics of North America* (Pain: Nociceptive and Neuropathic Mechanisms with Clinical Correlates). Philadelphia:W.B. Saunders Company. 1997:235-249.

Pain is normally secondary to activation of unencapsulated nerve endings that fire in response to stimulit that threaten or actually produce tissue damage.

[6] Saunders, C. Care of patients suffering from terminal illness at St. Joseph's Hospice. *Nursing Mirror*. February 14;1964:7-10.

[7] Woolf CJ, American College of Physicians, American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004:140:441-451. PMID: 15023710.

Review of recent pathophysiological data with goal of illustrating present and future pharmacological strategies to prevent and manage pain.

[8] WHO. Cancer pain relief. Second edition. Geneva: WHO, 1996.

[9] Principles of pain control in palliative care for adults. Guidance prepared by a working group of the Ethical Issues in Medicine Committee of the Royal College of Physicians. J R Coll Physicians Lond. Jul-Aug 2000;34(4):350-352.

This brief outline is intended to make the principles of pain control readily available to all clinicians who look after terminally ill patients. It applies to patients with non-malignant disease as well as to those with advanced cancer.

[10] Hanks GW, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer.* 2001;84(5):587-593. PMID: 11237376.

An expert working group of the European Association for Palliative Care has revised and updated its guidelines on the use of morphine and the alternative strong opioid analgesics which have been introduced in many parts of the world in recent years. The strength of the evidence on which each recommendation is based is indicated.

[11] Mitchell JR, Potter WZ. Drug metabolism in the production of liver injury.*Med Clin North Am.* 1975;59(4):877-885. PMID: 238084

Recent studies have demonstrated that many toxic drug reactions result from a common initiating event: the metabolic activation of chemically stable drugs to potent alkylating, arylating or acylating agents in the body. This review focuses on toxic drug reactions caused by metabolic activation presenting as a cell necrosis, neoplasia, and drug allergy.

[12] Michaelis M, Habler HJ, Jaenig W. Silent afferents: a separate class of primary afferents? *Clin Exp Pharmacol Physiol*. 1996;23(2):99-105. PMID: 8819636.

Fine sensory nerve fibres have been detected that are not excited by physiological stimuli, even at potentially tissue damaging intensities. Under inflammatory conditions some silent afferents are sensitized to physiological stimuli. The activation of silent afferents may lead to sensitization of nociceptive dorsal horn neurons.

[13] Yaksh TL. The spinal pharmacology of facilitation of afferent processing evoked by high-threshold afferent input of the postinjury pain state. *Curr Opin Neurol Neurosurg*. 1993;6(2):250-256. PMID: 8097639.

Repetitive C afferent input evokes a facilitated state of processing that results in increased receptive fields and exaggerated responses to afferent input ("wind-up"). These phenomena underlie the behavioral phenomena of secondary hyperalgesia. The initiation of this facilitated component is not well blocked by even higher concentrations of volatile anesthetics, but it can be prevented by pretreatment with agents known to block afferent input (local anesthetics) or C-fiber transmitter release (opiates) or to act at one of several links to block a complex spinal cascade involving the N-methyl-D-aspartate receptor, nitric oxide synthase, and cyclooxygenase.

[14] Carson JL, Willett LR. Toxicity of nonsteroidal anti-inflammatory drugs. An overview of the epidemiological evidence. *Drugs*. 1993;46 Suppl 1:243-248. Review. PMID: 7506183.

Meta-analysis has demonstrated that NSAIDs are associated with serious upper gastrointestinal disorders, with a relative risk of 2.7 in patients receiving NSAIDs compared with subjects not receiving NSAIDs. An increase in the dose and duration of NSAIDs and age > 60 are associated with an increase in the risk of upper gastrointestinal toxicity. Case-control studies have demonstrated an association between some NSAIDs and neutropenia, with a relative risk of between 3 and 9. NSAIDs have also been linked with hypersensitivity reactions, although the incidence of such reactions is very low. There are inconsistent data on the potential associations between NSAIDs and renal disease, and there are no epidemiological studies linking NSAIDs with acute liver disease.

[15] Peura DA. Gastrointestinal safety and tolerability of nonselective nonsteroidal anti-inflammatory agents and cyclooxygenase-2-selective inhibitors. *Cleve Clin J Med*. 2002;69 Suppl 1:SI31-139. Review. PMID: 12086291.

GI side effects of NSAIDs range from dyspepsia and gastroduodenal ulcers to serious, potentially fatal GI complications including bleeding and perforation. Risk assessment and cotherapy with acid suppressors (H2-receptor antagonists and proton pump inhibitors) or prostaglandin replacement (misoprostol) and H pylori eradication are beneficial. Cyclooxygenase-1 (COX-1) is a key enzyme in gastroprotective mucosal defenses, and the best way to prevent GI toxicity is to avoid drugs that inhibit COX-1. Clinical studies of the COX-2-selective inhibitors rofecoxib and celecoxib have demonstrated efficacy equivalent to nonselective NSAIDs with lower rates of GI side effects (for example, incidence of endoscopic ulcers equivalent to placebo).

[16] Farrar JT, Portenoy RK. Neuropathic cancer pain: the role of adjuvant analgesics. *Oncology*. 2001;15(11):1435-1445. PMID: 11758872.

The primary adjuvant analgesics are anticonvulsant and antidepressant medications, but a wide variety of other drugs are also used. To optimize analgesic therapy in patients with neuropathic pain, both opioid and adjuvant analgesics must be used effectively.

[17] Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther*. 1992;260(1):275-285. PMID: 1309873.

The antinociceptive activity of tramadol in the mouse tail-flick test was completely antagonized by naloxone, suggesting an opioid mechanism of action. In contrast to the mouse tail-flick test and unlike morphine or codeine, tramadol-induced antinociception in the mouse abdominal constriction, mouse hot-plate (48 degrees or 55 degrees C) or rat hot-plate tests was only partially antagonized by naloxone, implicating a nonopioid component. Tramadol inhibited the uptake of norepinephrine (Ki = 0.79 microM) and serotonin (0.99 microM). These results suggest that tramadol-induced antinociception is mediated by opioid (mu) and nonopioid (inhibition of monoamine uptake) mechanisms.

[18] Harati Y, Gooch C, Edelmann S, et al. Double blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology*. 1998;50:1842-1846. PMID: 9633738. Full Text

This multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group study enrolled a total of 131 patients with painful diabetic neuropathy and treated them with tramadol (n=65) or placebo (n=66). Tramadol, at an average dosage of 210 mg/day, was significantly (p < 0.001) more effective than placebo for treating the pain of diabetic neuropathy.

[19] Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs*. 1993;46(2):313-340. PMID: 7691519.

In patients with moderate to severe postoperative pain, intravenous or intramuscular tramadol has generally proved to be of equivalent potency to pethidine (meperidine) and one-fifth as potent as nalbuphine. Intravenous tramadol 50 to 150 mg was equivalent in analgesic efficacy to morphine 5 to 15mg in patients with moderate pain following surgery. Orally administered tramadol was found to be an effective analgesic in step 2 of the World Health Organization's analgesic ladder. Dizziness, nausea, sedation, dry mouth and sweating are the principal adverse effects. Respiratory depression has been observed in only a few patients after tramadol infusion.

[20] Mercadante S, Arcuri E. opioids and renal function. *The Journal of Pain*. 2004;5:2-19. PMID: 14975374.

Renal impairment has a serious impact on the clearance of most opioids used in the clinical setting. Biochemical and clinical monitoring will prevent complications.

[21] Pereira J, Bruera E. Emerging neuropsychiatric toxicities of opioids. *J Pharm Care Pain Symptom Control.* 1997;5(4):3-29.

[22] Collins SL, Faura CC, Moore RA, McQuay HJ. Peak plasma concentrations after oral morphine: a systematic review. *J Pain Symptom Manage*. 1998;16(6):388-402. PMID: 9879164. Full Text

A systematic review of 69 studies with information on 2146 subjects (454 patients and 1692 healthy volunteers) found minimal difference between single and multiple doses, suggesting no accumulation of morphine. For controlled-release formulations, little difference was observed between brands except for once-daily formulations where Tmax for fed subjects considerably longer than for fasted.

[23] Stuart-Harris R, Joel SP, McDonald P, Currow D, Slevin ML. The pharmacokinetics of morphine and morphine glucuronide metabolites after subcutaneous bolus injection and subcutaneous infusion of morphine. *Br J Clin Pharmacol*. 2000;49(3):207-214. PMID: 10718775. Full Text

Six healthy volunteers each received 5 mg morphine sulphate by i.v., s.c.b. and short s.c.i. over 4 h, on three separate occasions, in random order, each separated by at least 1 week. Bioequivalence was demonstrated.

[24] Verebely K, Volavka J, Mule S, Resnick R. Methadone in man: pharmacokinetic and excretion studies in acute and chronic treatment. *Clin Pharmacol Ther*. 1975;18(2):180-190. PMID: 1149368.

The biologic disposition of methadone in acute and during chronic administration was studied in 12 human volunteers. The acute primary half-life (t1/2) of 14.3 hr in combination with the acute secondary t1/2 of 54.8 hr were longer than the single exponential chronic t1/2 of 22.2 hr determined in the same subjects.

[25] Du X, Skopp G, Aderjan R. The influence of the route of administration: a comparative study at steady state of oral sustained release morphine and morphine sulfate suppositories. *Ther Drug Monit*. 1999;21(2):208-214. PMID: 10217341.

Steady state pharmacokinetics of morphine were investigated in 6 patients. There were no significant differences in the mean steady state concentrations of morphine, M3G, and M6G between the oral and rectal administrations ($p > 0.05$).

[26] Levy MH. Pharmacologic treatment of cancer pain. *N Engl J Med*. 1996;335:1124-1132. PMID: 8813044. Full Text

Thirty percent of patients with cancer have pain at the time of diagnosis, and 65 to 85 percent have pain when their disease is advanced. Cancer pain can be effectively treated in 85 to 95 percent of patients with an integrated program of systemic, pharmacologic, and anticancer therapy..

[27] Gourlay GK, Kowalski SR, Plummer JL, Cherry DA, Gaukroger P, Cousins MJ. The transdermal administration of fentanyl in the treatment of postoperative pain: pharmacokinetics and pharmacodynamic effects. *Pain*. 1989;37(2):193-202. PMID: 2748192.

Transdermal fentanyl was evaluated in 13 surgical patients after an abdominal operation. There was a mean delay time of 12.7 h before minimum effective blood fentanyl concentrations (MEC) were obtained from the systems and pseudo-steady state was reached between 36 and 48 h. There was a decay time of 16.1 (7.1) h after the systems were removed. There was marked variability between patients. Nausea was the most frequently reported side effect (85% of patients) while bradypnoea, drowsiness, unpleasant dreams and headache were also reported. Side effects due to the topical formulation were transient and included erythema (8 patients) and a minor rash (2 patients) in the area occluded by the systems.

[28] Streisand JB, Varvel JR, Stanski DR, Le Maire L, Ashburn MA, Hague BI, Tarver SD, Stanley TH. Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology*. 1991;75(2):223-229. PMID: 1859010.

12 volunteers were given intravenous fentanyl citrate or oral transmucosoal fentanyl 15 micrograms/kg or oral fentanyl solution to swallow. Peak absorption rate and systemic bioavailability was greater and occurred much sooner after OTF than after oral solution administration.

[29] Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, Mercadante S, Pasternak G, Ventafridda V; Expert Working Group of the European Association of Palliative Care Network. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol*. 2001;19(9):2542-2554. PMID: 11331334.

A substantial minority of patients treated with oral morphine (10% to 30%) do not have a successful outcome because of (1) excessive adverse effects, (2) inadequate analgesia, or (3) a combination of both excessive adverse effects along with inadequate analgesia. This study presents evidence-based recommendations for clinical-practice formulated by an Expert Working Group of the European Association of Palliative Care (EAPC)Research NETWORK.

[30] Pasternak GW. Incomplete cross tolerance and multiple mu opioid peptide receptors. *Trends Pharmacol Sci*. 2001;22(2):67-70. PMID: 11166849. Full Text

One explanation for incomplete cross tolerance at the mu opioid receptor could be the presence of multiple receptor subtypes; at least seven different splice variants have been isolated.

[31] 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(2):73-83. PMID: 11305074. Full Text

Methadone, a synthetic opioid, has unique pharmacodynamics and pharmacokinetics, which contribute to its unique ability to relieve pain unresponsive to other potent opiates. Several guidelines of administration have been established.

[32] Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. *Pain*. 1997;70(2-3):109-15. PMID: 9150283.

Methadone has a number of unique characteristics including excellent oral and rectal absorption, no known active metabolites,high potency, low cost, and longer administration intervals, as well as an incomplete cross-tolerance with respect to other mu-opioid receptor agonist drugs. Its use is limited by the remarkably long and unpredictable half-life, large inter-individual variations in pharmacokinetics, the potential for delayed toxicity, and above all by the limited knowledge of correct administration intervals and the equianalgesic ratio with other opioids when administered chronically.

[33] Vigano A, Fan D, Bruera E. Individualized use of methadone and opioid rotation in the comprehensive management of cancer pain associated with poor prognostic indicators. *Pain*. 1996;67(1):115-119. PMID: 8895238. Full Text

This case report describes a decrease of the morphine equivalent daily dose (MEDD) from 1050 to 36 after rotation to methadone.

[34] Backonja M, Beydoun A, Edwards K, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280:1831-1836. PMID: 9846777. Full Text

8-week trial of gabapentin (titrated from 900 to 3600 mg/d or maximum tolerated dosage) or placebo. By intent-to-treat analysis, gabapentin-treated patients' mean daily pain score at the study end point

(baseline, 6.4; end point, 3.9; n = 82) was significantly lower (P<.001) compared with the placebo-treated patients' end-point score (baseline, 6.5; end point, 5.1; n = 80).

[35] Caraceni A, Zecca E, Bonezzi C et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the gabapentin cancer pain study group. *J Clin Oncol*. 2004;22:2909-2917. PMID: 15254060. Full Text

121 consecutive patients with neuropathic pain due to cancer, partially controlled with systemic opioids, treated with gabapentin titrated from 600 mg/d to 1,800 mg/d in addition to stable opioid dose. Analysis of covariance (ANCOVA) on the intent-to-treat population showed a significant difference of average pain intensity between gabapentin (pain score, 4.6) and placebo group (pain score, 5.4; P =.0250).

[36] Caccia MR. Clonazepam in facial neuralgia and cluster headache. Clinical and electrophysiological study. *Eur Neurol*. 1975;13(6):560-563. PMID: 1104361.

Clonazepam seems to be an effective drug in idiopathic trigeminal neuralgia. Electrophysiological investigations support the idea that this neuralgia is due to a loss of central inhibition. During the first 1-2 weeks of treatment marked drowsiness is observed in the majority of cases. In one case, presence of a synergism between Clonazepam and L-dopa+ inhibitor was also observed.

[37] McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *BMJ*. 1995;311(7012):1047-1052. PMID: 7580659. Full Text

Systematic review of 20 randomised controlled trials of anticonvulsants for acute, chronic, or cancer pain. For treating trigeminal neuralgia, carbamazepine had a combined number needed to treat of 2.6 for effectiveness, 3.4 for adverse effects, and 24 for severe effects (withdrawal from study). For treating diabetic neuropathy, anticonvulsants had a combined number needed to treat of 2.5 for effectiveness, 3.1 for adverse effects, and 20 for severe effects. For migraine prophylaxis, anticonvulsants had a combined number needed to treat of 1.6 for effectiveness, 2.4 for adverse effects, and 39 for severe effects.

[38] Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. *Neurology*. 2001;57(3):505-509. PMID: 11502921. Full Text

59 patients received either lamotrigine (titrated from 25 to 400 mg/day) or placebo over a 6-week period. Daily numerical pain score in the lamotrigine-treated group was reduced from 6.4 +/- 0.1 to 4.2 +/- 0.1 and in the control group from 6.5 +/- 0.1 to 5.3 +/- 0.1 (p < 0.001 for lamotrigine doses of 200, 300, and 400 mg).

[39] Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med*. 1992;326(19):1250-1256. PMID: 1560801.

Two randomized, double-blind, crossover studies in patients with painful diabetic neuropathy, comparing amitriptyline with the relatively selective blocker of norepinephrine reuptake desipramine in 38 patients, and comparing the selective blocker of serotonin reuptake fluoxetine with placebo in 46 patients. Desipramine relieves pain with efficacy similar to that of amitriptyline. Fluoxetine, which blocks serotonin uptake, is no more effective than placebo.

[40] Eisenach JC, Gebhart GF. Intrathecal amitriptyline acts as an N-methyl-D-aspartate receptor antagonist in the presence inflammatory hyperalgesia in rats. *Anesthesiology*. 1995;83:1046-1054. PMID: 7486155. Full Text

Amitriptyline reverses hyperalgesia in rats by a mechanism unrelated to monoamine reuptake inhibition, and likely due to NMDA receptor antagonism.

[41] Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology*. 1998;51(4):1166-1171. PMID: 9781549. Full Text

A randomized, double-blind, crossover trial in 33 patients. Pain relief occurred without an antidepressant effect, and that although there were fewer side effects with nortriptyline, amitryptiline and nortriptyline have a similar analgesic action for most individuals.

[42] Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. *Eur J Pain*. 2002;6(1):17-24. PMID: 11888224. Full Text

A randomized, double-blind, crossover comparison of venlafaxine and inactive placebo in 13 patients. The average daily pain intensity as reported in the diary (primary outcome) was not significantly reduced by venlafaxine compared with placebo. However, the average pain relief (diary) and the maximum pain intensity (retrospective assessment by the computer program) were significantly lower with venlafaxine compared with placebo.

[43] Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic *neuralgia. Neurology.* 1997;48(5):1212-1218. PMID: 9153445. Full Text

Two randomized, double-blind, crossover trials comparing six weeks of *oral* dextromethorphan to placebo. Mean doses were 381 mg/day in diabetics and 439 mg/day in postherpetic neuralgia patients. In diabetic neuropathy, dextromethorphan decreased pain by a mean of 24% (95% CI: 6% to 42%, p = 0.01), relative to placebo. In postherpetic neuralgia, dextromethorphan did not reduce pain.

[44] Galer BS, Harle J, Rowbotham MC. Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: a prospective study. *J Pain Symptom Manage*. 1996;12(3):161-167. PMID: 8803379. Full Text

Prospective study of nine subjects with chronic neuropathic pain of peripheral origin treated with intravenous lidocaine, 2 mg/kg and 5 mg/kg, over 45 min during separate sessions in random order under double-blind conditions. Subsequent response to oral mexiletine was significantly correlated with the average response to the two IVL.

[45] Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain*. 1996;65(1):39-44. PMID: 8826488. Full Text

Thirty-five subjects with established post-herpetic neuraligia affecting the torso or extremities completed a four-session, random order, double-blind, vehicle-controlled study of the analgesic effects of topically applied 5% lidocaine in the form of a non-woven polyethylene adhesive patch. All subjects had allodynia on examination. Up to 3 patches, covering a maximum of 420 cm2, were applied to cover the area of greatest pain as fully as possible. Lidocaine containing patches significantly reduced pain intensity at all time points 30 min to 12 h compared to no-treatment and vehicle only treatment.

[46] Eisenach JC, Rauck RL, Buzzanell C, Lysak SZ. Epidural clonidine analgesia for intractable cancer pain: phase I. *Anesthesiology*. 1989;71(5):647-652. PMID: 2817457.

Clonidine (range, 100-900 micrograms in 100-micrograms increments) was injected in nine patients and produced analgesia, as measured by change in verbal pain scores, lasting more than 6 h. Clonidine also decreased blood pressure, although this effect was well tolerated and no patient met criteria for receiving iv ephedrine (greater than 30% decrease in mean arterial pressure not responsive to 500 ml iv crystalloid infusion). Clonidine decreased heart rate 10-30% and produced transient sedation.

[47] North RA, Williams JT, Surprenant A, Christie MJ. Mu and delta receptors belong to a family of receptors that are coupled to potassium channels. *Proc Natl Acad Sci U S A*. 1987;84(15):5487-5491. PMID: 2440052. Full Text

The mu and delta opioid receptors appear to be unusual in that both utilize a potassium conductance mechanism similar to other neurotransmitter receptors.

[48] Yaksh TL, Pogrel JW, Lee YW, Chaplan SR. Reversal of nerve ligation-induced allodynia by spinal alpha-2 adrenoceptor agonists. *J Pharmacol Exp Ther*. 1995;272(1):207-214. PMID: 7815335.

Lumbar intrathecal injection of alpha-2, but not alpha-1 or an opiate agonist, resulted in a dose-dependent reversal of the allodynia in rats. The failure of morphine to exert an antiallodynic action reflects the fact that 1) opiates act presynaptically on small primary afferents and the allodynia is mediated by large afferent input and 2) opiates, unlike alpha-2 agonists do not have an effect on autonomic outflow.

[49] Swartz SL, Dluhy RG. Corticosteroids: clinical pharmacology and therapeutic use. *Drugs*. 1978;16(3):238-255. PMID: 209958.

The enhanced anti-inflammatory activity of the various synthetic analogues of cortisol is not dissociated from the expected catabolic actions of glucocorticoid hormones. With improvement of the underlying disorder, the steroid dosage can be rapidly tapered and then discontinued over a 2 to 3 day period. After more than 2 weeks of treatment, suppression of the hypothalamic-pituitary-adrenal axis may persist for as long as 9 to 12 months. The steroid dosage should also be given as a single morning dose if possible.

[50] Demoly P, Chung KF. Pharmacology of corticosteroids. *Respir Med*. 1998;92(3):385-394. PMID: 9692094.

The available data on glucocorticoids for the treatment of asthma is reviewed.

[51] Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. *Drug Saf*. 2000;22(2):111-122. PMID: 10672894.

Several serious psychiatric syndromes can be rarely caused by corticosteroids: substance-induced mood disorders (with depressive, manic and mixed features), substance-induced psychotic disorders and delirium. A variety of pharmacological strategies for treatment and prevention have been proposed.

[52] Sorensen S, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomised trial. *Eur J Cancer*. 1994;30A(1):22-27. PMID: 8142159.

A randomized single blind trial of high-dose dexamethasone as an adjunct to radiotherapy in 57 patients with metastatic spinal cord compression from solid tumours. Dexamethasone was administered as a bolus of 96 mg intravenously, followed by 96 mg orally for 3 days and then tapered in 10 days. A successful treatment result defined as gait function after treatment was obtained in 81% of the patients treated with dexamethasone compared to 63% of the patients receiving no dexamethasone therapy. Six months after treatment, 59% of the patients in the dexamethasone group were still ambulatory compared to 33% in the no dexamethasone group. Median survival was identical in the two treatment groups.

[53] Coleman RE. Management of bone metastases. *Oncologist*. 2000;5(6):463-470. PMID: 11110597.

External beam radiotherapy and systemic endocrine and cytotoxic treatments are the mainstay of treatment in advanced cancers. Bisphosphonates provide an additional treatment strategy.

[54] Blum RH, Novetsky D, Shasha D, Fleishman S. The multidisciplinary approach to bone metastases. *Oncology*. 2003;17:845-857. PMID: 12846127.

A comprehensive review of the multimodality treatment available for patients with bone mets. Pain management, including the adjuvant modalities of bisphosphonates, corticosteroids, calcitonin, radiopharmaceuticals, and NSAIDs, is discussed.

[55] McNicol E, Morowicz-Mehler N, Risk RA, Bennett K, Gialeli-Goudas M, Chew PW, Lau J, Carr D. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *The Journal of Pain*. 2003;4:231-256. PMID: 14622694. Full Text

A systematic review of 67 trials to assess the management of opioid side effects; constipation, pruritus, nausea and vomiting, myoclonus, sedation, respiratory depression, and delirium. Opioid rotation to manage side effects was also studied. The lack of well-designed, randomized controlled trials and the heterogeneity of populations and study designs made the drawing of firm conclusions difficult and precluded performance of meta-analysis.

[56] Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain*. 2001;93:247-257. PMID: 11514084. Full Text

Survey of symptom prevalence, etiology and severity in 593 cancer patients treated by a pain service. Efficacy of pain treatment was good in 70%, satisfactory in 16% and inadequate in 14% of patients. Prevalence and severity of anorexia, impaired activity, confusion, mood changes, insomnia, constipation, dyspepsia, dyspnoea, coughing, dysphagia and urinary symptoms were significantly reduced, those of sedation, other neuropsychiatric symptoms and dry mouth were significantly increased and those of coma, vertigo, diarrhea, nausea, vomiting, intestinal obstruction, erythema, pruritus and sweating remained unchanged. The most frequent symptoms were impaired activity (74% of days), mood changes (22%), constipation (23%), nausea (23%) and dry mouth (20%). Of all 23 symptoms, only constipation, erythema and dry mouth were assessed as being most frequently caused by the analgesic regimen.

[57] Miaskowski C, Dodd MJ, West C, et al. Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management. *Journal of Clinical Oncology*. 2001;19:4275-4279. PMID: 11731509.

A random sample of 65 adult oncology outpatients with a Karnofsky performance status score of >or= 50, an average pain intensity score of >or= 2.5, and radiographic evidence of bone metastasis were recruited for this longitudinal study from seven outpatient setting. Adherence rates for opioid analgesics prescribed on an around-the-clock basis ranged from 84.5% to 90.8% and on an as-needed basis from 22.2% to 26.6%.

[58] O'Mahony S, Coyle N, Payne R. Current Management of Opioid-Related Side Effects. *Oncology*. 2001;15(1):61-82. PMID: 11271983.

This article reviews the current optimal management of opioid-related nausea and vomiting, constipation, cognitive side effects, myoclonus, and respiratory depression.

[59] DuPen SL, DuPen AR, Polissar N, et al: Implementing Guidelines for Cancer Pain Management: Results of a Randomized Controlled Clinical Trial. *Journal of Clinical Oncology*. 1999;17:361-370. PMID: 10458255.

81 cancer patients, aged 37 to 76 years, were enrolled onto a prospective, longitudinal, randomized controlled study from the outpatient clinic settings of 26 western Washington-area medical oncologists. Patients randomized to the pain algorithm group achieved a statistically significant reduction in usual pain intensity, measured as slope scores, when compared with standard community practice (P < .02).

[60] Smith TJ, Staats PS, Deer T, et al: Randomized Clinical Trial of an Implantable Drug Delivery System Compared with Comprehensive Medical management for Refractory Cancer Pain: Impact on Pain, Drug-Related Toxicity, and Survival. *Journal of Clinical Oncology*. 2002;20:4040-4049. PMID: 12351602. Full Text

In a randomized clinical trial of 202 patients with unrelieved pain (visual analog scale (VAS) pain scores ≥5 on a 0-10 scale) on at least 200 mg or morphine oral equivalent daily, implanted intrathecal therapy reduced pain, relieved common drug toxicities, and were associated with improved survival in patients with refractory cancer pain. Reductions in fatigue, confusion, sedation, personality changes, constipation, vomiting, and urticaria were noted. Survival was also improved with 17 more patients of every 100 estimated to be alive at 6 months.

[61] Staats PS: The pain-mortality link: Unraveling the mysteries, in Payne R, Patt RH, Hill CS (eds): Assessment and treatment of cancer pain. Progression in pain research and management. Seattle, IASP Press; 1998:145-156.

[62] Liebeskind JC. Pain can kill. *Pain*. 1991;44:3-4. PMID: 2038486.

Summarizes evidence that pain of sufficient magnitude can, directly or indirectly, suppress immune mechanisms normally serving to defend the body against tumors, and can thereby cause a marked increase in tumor growth.

[63] Gupta K, Kshirsagar S, Chang L, et al: Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. *Cancer Research*. 2002;62:4491-4498. PMID: 12154060.

Morphine, in a concentration typical of that observed in patients' blood, stimulates human microvascular endothelial cell proliferation and angiogenesis in vitro and in vivo.

[64] Staats P, Hekmat H, Sauter P, Lillemoe K: The Effects of Alcohol Celiac Plexus Block, Pain, and Mood on Longevity in Patients With Unresectable Pancreatic Cancer: A Double-blind, Randomized, Placebo-controlled study Study. *Pain Medicine*. 2001;2(1):28-34. PMID: 15102315.

130 patients with histologically proven, unresectable pancreatic cancer received either an alcohol or a saline block. The neurolytic block, as compared with medical management alone, improved pain, elevated mood, reduced pain interference with activity, and was associated with an increase in life expectancy.

[65] DeVulder J, Ghys L, Dhondt W, Rolly G. Spinal Analgesia in Terminal Care: Risk versus Benefit. *J Pain Symptom Manage*. 1994;9:75-81. PMID: 8021538

In a population of 92 cancer patients, 13 received intrathecal morphine. The generally accepted indications for the technique appeared to be justified. Three patients developed meningitis.

[66] Hassenbusch S, Pillay P, Magdinec M, et al. Constant infusion of morphine for intractable cancer pain using an implanted pump. *J Neurosurgery*. 1990;73:405-409. PMID: 2384779.

26 cases of chronic intrathecal morphine administration are described. The average duration was 132 days. The efficacy of the method was excellent: 23 of 26 patients used no other analgesics or only minor ones such as aspirin, paracetamol, or dextropropoxyphene. There were no infections under and only 4 catheter blockages (1 by tumor).

[67] Onofrio B, Yaksh T. Long-term pain relief produced by intrathecal morphine infusion in 53 patients. *J Neurosurgery*. 1990;72:200-209. PMID: 1688618.

The median postimplant survival time was 4 months.

[68] Penn R, Paice J. Chronic intrathecal morphine for intractable pain. *J Neurosurgey*. 1987;67:182-186. PMID: 3598678.

Forty-three patients with intractable pain received intrathecal morphine delivered by implanted continuous-infusion devices. In 35 patients the pain was due to cancer, and eight patients had chronic

nonmalignant pain. Twenty-eight (80%) of the patients with cancer-related pain experienced excellent or good relief. Side effects were rare.

[69] Gestin Y, Vainio A, Pegurier AM. Long-term intrathecal infusion of morphine in the home care of patients with advanced cancer. *Acta Anaesthesiol Scand.* 1997;41:12-17. PMID: 9061109.

50 patients having refractory cancer pain were treated with a continuous intrathecal infusion of morphine using an external pump with patient-controlled boluses. In this retrospective study, the average duration of intrathecal infusion was 142 (7-584) days. The mean starting dose, 2.5 (0.4-8.3) mg/day, increased to a mean final dose of 9.2 (1-94) mg/day, the average dose being 5.4 (1-23) mg/day. During the treatment period, no clinically detectable infections and no respiratory depression occurred. Leakage of cerebrospinal fluid followed by post-spinal headache occurred in only 6 patients.

[70] Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain.* 1995;61(2):277-284. PMID: 7659438.

3 distinct levels of pain severity that can be defined on a 0-10-point numerical scale. Based on the degree of interference with cancer patients' function, ratings of 1-4 correspond to mild pain, 5-6 to moderate pain, and 7-10 to severe pain. Our analysis illustrates that the pain severity-interference relationship is non-linear.

[71] Hogan Q, Haddox JD, Abram S, Weissman D, Taylor ML, Janjan N. Epidural opiates and local anesthetics for the management of cancer pain. *Pain.* 1991;46(3):271-279. PMID: 1758711.

16 patients out of 1205 cancer patients received epidural therapy. Although analgesia was obtained in all 16, complications occurred in 11 of the 16 patients, including dislodged or broken catheters, pain on injection, bleeding/bruising or infection.

[72] Smitt PS, Tsafka A, Teng-van de Zande F, et al: Outcome and complications of epidural analgesia in patients with chronic cancer pain. *Cancer.* 1998;83:2015-2022. PMID: 9806662. Full Text

Epidural analgesia gave adequate pain relief in 76% of 91 patients who received it, but complications occurred in 43% of patients, such that the authors did not recommend it for patients with more than 3 months to live.

[73] Nitescu P, Dahm P, Appelgren L, and Curelaru I. Continuous infusion of opioid and bupivacaine by externalized intrathecal catherters in long-term treatment of "refractory" nonmalignant pain. *Clin J Pain.* 1998;14(1):17-28. PMID: 9535310. Full Text

Prospective, cohort, nonrandomized, consecutive trial. of 90 patients, 40 men and 50 women, 20 to 96 years old (median, 70 years), with various nonmalignant "refractory" pain conditions lasting for 0.3 to 50 years (median, 3 years). During the intrathecal period [range, 3-1,706 days; median, 60 days; totaling 14,686 days, 7,460 (50% of which were spent at home)], 86 patients (approximately 95%) obtained acceptable (60-100%) pain relief.

[74] Sharfman WH, Walsh TD. Has the analgesic efficacy of neurolytic celiac plexus block been demonstrated in pancreatic cancer pain. *Pain.* 1990;41:267-271. PMID: 1697055.

Reviewed 15 published series since 1964A total of 480 patients with cancer of the pancreas were reported; at least a satisfactory response to NCPB was reported in 418 (87%). We found major deficiencies in these reports.

[75] Polati E, Finco G, Gottin L, Bassi C, Pederzoli P, Ischia S. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. *Br J Surg.* 1998;85:199-201. PMID: 9501815. Full Text

Twenty-four patients were divided into two groups: 12 patients underwent NCPB (group 1) and 12 were treated with pharmacological therapy (group 2). Immediately after the block, patients in group 1 reported significant pain relief compared with those in group 2 ($P < 0.05$), but long-term results did not differ between the groups. Mean analgesic consumption was lower in group 1.

[76] Chambers PC. Coeliac plexus block for upper abdominal cancer pain. *British Journal of Nursing.* 2003;12:838-844. PMID: 12951534. Full Text

CPB is a relatively safe procedure, and although it is associated with common adverse effects such as diarrhoea, hypotension and local pain, these are mostly transient. However, severe complications, including paraplegia, have been reported.

[77] Lillemoe K, Cameron JL, Kaufman HS, Yeo CJ, Pitt HA, Sauter PK. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. *Annals of Surgery.* 1993:447-455. PMID: 7683868.

Chemical splanchnicectomy with alcohol was performed in 65 patients, whereas 72 patients received the placebo. No differences in hospital mortality or complications, return to oral intake, or length of hospital stay were observed. Mean pain scores were significantly lower in the alcohol group at 2-, 4-, and 6-month follow-up and at the final assessment ($p < 0.05$). Furthermore, patients with preexisting pain who received alcohol showed a significant improvement in survival when compared with controls ($p < 0.0001$).

[78] Davis CL, Lam W, Roberts M, Daniels J, Joel SP, Slevin ML: The pharmacokinetics of nebulised morphine. *Proceedings of the International Association for the Study of Pain.* 1993;379:(Abstract).

[79] Lamer T. Treatment of Cancer-Related Pain; When Orally Administered Medications Fail. *Mayo Clin Proc.* 1994;69:473-480. PMID: 8170201.

When orally administered medications fail to control pain or cause excessive side effects, patients should be referred to an appropriate specialist or medical center for consideration of other pain-relieving techniques.

[80] Hanekop GG, Bautz MT, Beck D, Kettler D, Ensink FB. Pain therapy in tumor patients and in palliative medicine: 2: Invasive measures. *Zentralbl Chir.* 1998;123:664-677. PMID: 9703641.

Physicians tend to treat pain as a completely somatic disorder, but chronic pain states are always bio-psycho-social in nature. Anesthesiological and neurosurgical procedures are only a part of the possible and necessary treatment options.

[81] Arter OE, Racz GB. Pain management of the oncologic patient. *Semin Surg Oncol.* 1990;6:162-172. PMID: 2189196.

Neurolytic procedures should be performed prior to initiation of high dose narcotic therapy, radiation, chemotherapy, and surgery when possible.