

### **PART III: ADJUVANTS, ADVERSE EFFECTS, BARRIERS**

#### **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 (e.g., tricyclic antidepressant medications for postherpetic neuralgia)
- They can be added into the pain management plan at any step in the WHO ladder

#### **Neuropathic Pain Management. Burning, Tingling Neuropathic Pain**

- Neuropathic pain often requires an adjuvant analgesic in addition to an opioid to adequately manage the pain
- For patients who describe their neuropathic pain as "burning" or "tingling" with or without associated numbness, the first choice is usually:
  - Tricyclic antidepressant or
  - Gabapentin
- The SSRIs (selective serotonin reuptake inhibitors):
  - Have shown disappointing clinical efficacy as analgesics
  - Are less effective as adjuvants to manage neuropathic pain than the tricyclic antidepressants

#### **Tricyclic Antidepressants for Burning Pain**

##### **Amitriptyline - Advantages**

- Amitriptyline is the most extensively studied of the tricyclic antidepressants
- In contrast to its antidepressant effects, low doses beginning at 10 to 25 mg orally at bedtime may be effective in only a few days
  - The dose may be escalated every 4 to 7 days until pain relief or adverse effects intervene
  - It may take high doses and a few weeks to control the pain

##### **Amitriptyline - Adverse Effects**

- Increased risk of toxicity at doses greater than 100 mg/24 hours
  - Need to monitor plasma drug levels to watch for toxicity
- Prominent anticholinergic activity
- Risk of cardiac toxicity
- Sedating effect
  - May be helpful to the patient who is also having difficulty sleeping
  - Limits its use in many frail and elderly patients

##### **Amitriptyline Alternatives**

###### **1. Desipramine**

- Minimal anticholinergic or sedating adverse effects
- Dosing is the same as for amitriptyline
- Its adverse effect profile may make it the tricyclic of choice, particularly in the frail and seriously ill

###### **2. Nortriptyline**

- May also be effective in pain management

- Has less adverse effects than amitriptyline

### **Gabapentin for Burning Pain**

- Gabapentin, a new anticonvulsant, appears to be quite effective as an adjuvant for all types of neuropathic pain
- Its site and mode of action are not clear
- Most clinicians:
  - Begin at low doses (100 mg po q d to tid)
  - Dose escalate every 1 to 2 days by 100 mg po tid to effect
- Usual effective dose 900–1800 mg/day
  - Some patients require doses of more than 3600 mg/day
- Adverse effects appear to be minimal
- While some patients experience drowsiness with dose escalation, tolerance appears to develop within a few days if the dose remains stable

### **Shooting, Stabbing Pain**

- For episodic shooting, stabbing, electrical pain, the anticonvulsants gabapentin, carbamazepine, and valproic acid are the most widely used adjuvant medications
- Gabapentin
  - Start at 100 mg po q d to tid
  - Increase by 100 mg every 1 to 2 days to effect
- Carbamazepine
  - Start at 100 mg po bid to tid
  - Increase by 100 to 200 mg every 5 to 7 days to effect
- Valproic acid
  - Start at 250 mg po q hs VA
  - Increase by 250 mg every 7 days in divided doses to effect
- As doses escalate, monitoring carbamazepine or valproic acid plasma levels may help to predict increasing risk of adverse effects

### **Complex Neuropathic Pain**

- As nerve damage evolves, the resulting pain can become mixed and very complex to manage
- Nerve damage and chronic pain can lead to:
  - Primary neuronal death
  - Loss of myelin sheath
  - Central sensitization
  - Changes in the effective neurotransmitters and neuroreceptors
  - Sensory neuronal death
- Over time:
  - Opioid receptors may be down-regulated, making opioids much less effective
  - NMDA (N-methyl d-aspartate) receptors may become much more important as glutamate becomes a significant neurotransmitter
- While opioids may continue to be partially effective, adjuvant analgesic medications may be required, including:
  - Oral antiarrhythmics
  - Alpha-2 adrenergic agonists
  - NMDA receptor antagonists
  - Corticosteroids
- Consider consulting with a pain management expert early to minimize patient suffering and the risk of further damage from pain itself

### **Bone Pain: What is Bone Pain and What Causes It?**

- Bone pain is a frequently occurring problem that may be:
- It is frequently the result of mechanical changes due to metastases, compression or pathologic fracture, etc.

- Constant at rest
- Much worse with movement
- 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

### **Management of Bone Pain**

- Opioids remain the mainstay of bone pain management
- Significant additional relief may be provided by:
  - NSAIDs
  - Corticosteroids
  - bisphosphonates (e.g., alendronate, pamidronate)
  - Calcitonin
  - radiopharmaceuticals (e.g., strontium, samarium)
  - external beam radiation
- When definitive orthopedic interventions are not possible, external mechanical supports (splints, braces, etc) may provide relief from movement-related pain
- Consultation with a pain management expert may be necessary to achieve adequate relief

### **Pain From Bowel Obstruction: What is Pain from Bowel Obstruction and What Causes It?**

- Mechanical bowel obstruction can lead to significant abdominal pain as the bowel wall is stretched or inflamed. May be caused by:
  - Internal blockage from constipation
  - External compression by tumor or scars
- The pain is frequently described as constant, sharp, and cramping
- It may be associated with other unpleasant symptoms including:
  - Bloating
  - Distention
  - Gas
  - Nausea/vomiting

### **Management of Pain from Bowel Obstruction**

- In some cases, definitive intervention may be possible, such as:
  - Relief of constipation (see Module 10: Common Physical Symptoms)
  - Surgical removal or bypass of external blockages
- While some people will find opioids sufficient to manage this pain, many will need adjuvant medications to effectively relieve their discomfort. Consider using adjuvants such as:
  - Corticosteroids
  - NSAIDs
- Anticholinergic medications (e.g., 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

### **Corticosteroids in Pain Management: Uses of Corticosteroids**

- Corticosteroids are frequently helpful and commonly used in advanced illness
- They may be useful for a variety of symptoms, including:
  - Acute nerve compression
  - Increased intracranial pressure
  - Bone pain
  - Visceral pain (obstruction of a viscous and/or capsular distention)
  - Anorexia
  - Nausea

- Depressed mood

### Drug and Dosage Recommendations

- Dexamethasone is the drug of choice due to its:
  - Long half-life (>36 hours)
  - Minimal mineralocorticoid effect
- It can be administered once a day in doses of 2 to 20 mg or more

### Adverse Effects

- Steroid psychosis should be considered if an agitated delirium ensues
- Other toxicities that are possible with long-term use but are seldom a problem in the setting of advanced disease include:
  - Proximal myopathy
  - Oral candidiasis
  - Bone loss

### Topical Analgesia in Pain Management

- 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

### Anesthesia, Neurosurgery in Pain Management

- For difficult to manage, persistent pain, anesthesia or neurosurgical colleagues may be able to provide considerable pain relief through:
  - Nerve blocks
  - Unilateral cordotomies
  - Other selective procedures
- Consider referring patients with:
  - Upper abdominal pain due to pancreatic disease
  - Lower body pain
  - Pain localized to 1 limb
  - Unilateral pain

### Opioid Adverse Effects

- Opioids have many possible adverse effects; some are common, some not
- 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 is discussed in Module 10: Common Physical Symptoms
- Adverse effects should also be distinguished from 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

## Common Adverse Effects

- Constipation
- Dry mouth
- Nausea/vomiting
- Sedation
- Sweats

## Uncommon Adverse Effects

- Bad dreams/hallucinations
- Dysphoria/delirium
- Myoclonus/seizures
- Pruritus/urticaria
- Respiratory depression
- Urinary retention

## Constipation: What Causes Opioid-Related Constipation?

- Constipation secondary to opioid administration is almost universal
- It is primarily the result of opioid effects on the CNS, spinal cord, and myenteric plexus of gut that, in turn:
  - Reduce gut motor activity
  - Increase stool transit time
- The colon has more time to desiccate its contents, leaving large hard stools that are difficult to pass
- Other factors that may make the problem worse include:
  - Dehydration
  - Poor food intake
  - Other medications

## Prevention and Management of Opioid-Related Constipation

- Tolerance to constipation may develop very slowly, if at all
- It requires anticipatory and ongoing management
- Dietary interventions alone (e.g., increase fluid and fiber) are often insufficient
- Bulk-forming agents (e.g., psyllium)
  - Require substantial fluid intake
  - Not recommended for those with advanced disease and poor mobility
- To counteract the slowing effect of opioids:
  - Start by prescribing a routine stimulant laxative (e.g., senna, bisacodyl, glycerine, casanthranol, etc)
  - Escalate the dose to effect
- While stool softeners (e.g., docusate sodium) are not usually effective by themselves, combination stimulant/softeners (e.g., senna + docusate sodium or calcium) can be useful
- Prokinetic agents (e.g., 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 Module 10: Common Physical Symptoms)

## Nausea, Vomiting

- Many patients starting opioids experience nausea with or without vomiting
  - Young women seem to be most at risk
- These symptoms:
  - Are easily anticipated and treated with antiemetics
  - Usually disappear as tolerance develops within a few days

- Dopamine-blocking agents are most often effective
  - prochlorperazine 10 mg before opioid and q 6h
  - haloperidol 1 mg before opioid and q 6h
  - metoclopramide 10 mg before opioid and q 6h
- In refractory cases, a more aggressive approach or an alternative opioid may become necessary

### **Sedation: Typical Course and Resolution of Sedation**

- Patients sometimes complain of feeling sedated or mentally clouded immediately after beginning an opioid analgesic
- Care must be taken to distinguish between:
  - True sedation (inability to fully wake up)
  - Exhaustion due to previous sleep deprivation with the unrelieved pain (sleeps a lot, but is able to fully wake up in between)
- 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

### **Sedation in Patients with Advanced Illness**

- For patients with very advanced disease, mental clouding and excessive somnolence are often issues
- This is particularly true 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

### **Management of Sedation**

- If sedation occurs:
  - Encourage patients and families to clearly articulate their goals (see Module 7: Goals of Care)
  - Develop a pain management plan that balances alertness and pain control to suit the individual
    - Some patients may prefer to be sleepy and comfortable
    - Others may prefer to be 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 (e.g., methylphenidate 5 mg q am and q noon and titrate), particularly if the opioid is providing effective analgesia

### **Dysphoria/Delirium**

- Delirium due to opioid excess may be suggested with the onset of:
  - Confusion
  - Bad dreams
  - Hallucinations
  - Restlessness
  - Agitation
  - Myoclonic jerks
  - Significantly depressed level of consciousness
  - Seizures
- Opioid-induced delirium rarely occurs when:
  - Opioid dosing guidelines are followed closely
  - Patients have normal renal clearance
- However, one or more of these adverse effects may present:
  - Gradually, in the patient who is not passing much urine and is accumulating opioid due to decreased intake or dehydration
  - Rapidly, in the patient who is developing sepsis

## Pruritus/Urticaria

- 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, non-sedating antihistamines while opioid dosing continues
  - fexofenadine 60 mg po bid
  - diphenhydramine, loratadine, or doxepin 10-30 mg po qhs

## Respiratory Depression. Common Myths about the Respiratory Depression with Opioid Use

**Myth #1:** The risk of respiratory depression when using opioids to relieve pain is high

### The Facts:

- The inappropriate application of animal and human models from acute pain research is in part responsible for this common fear
- Pain is a potent stimulus to breathe
- 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

**Myth #2:** As doses increase, respiratory depression can occur suddenly in the absence of overdose

### The Facts:

- Somnolence always precedes respiratory depression
- Adequate ongoing assessment and appropriate titration of opioids based on pharmacological 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

## Management of Respiratory Depression

- If respirations are compromised (< 6/minute), 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 min) due to 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
- If delirium due to opioid excess does occur, but respirations are not compromised (> 6/minute):
  - Routine opioids may be stopped
  - Treat the underlying cause of the adverse effects until they abate:
    - Ensure appropriate hydration
    - Manage sepsis

## Nonpharmacologic 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
    - TENS (transcutaneous electrical nerve stimulation)
    - acupuncture
  - Physical therapy
    - therapeutic exercises
    - heat and cold
  - Psychological approaches
    - cognitive therapies
    - relaxation, imagery, hypnosis
    - biofeedback
    - behavior therapy
    - psychotherapy
  - Art or music therapy
  - Massage, body work, etc
- Members of the interdisciplinary team, who may be more familiar with nonpharmacologic interventions, can frequently assist the physician to identify and refer patients appropriately

### **Barriers to Effective Pain Management**

- Today, pain management remains inadequate in spite of the fact that we have possessed information discussed in this module for over 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
  - Inappropriate regulatory oversight
- To be effective, individual care plans must:
  - Encourage patients to report their pain freely
  - 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

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