

## Pharmacotherapy of Pain

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## Objectives

- List common reasons for inadequate pain control
- Define pain
- Formulate a rational approach to the assessment and treatment of pain
- Describe pain assessment
- Name the analgesic drugs used in pain management and describe appropriate doses, adverse effects, drug interactions and patient counseling considerations

## Pain Myths

- Pain is an inevitable and untreatable consequence of cancer
- Pain medication is usually addictive
- Reporting pain is a sign of weakness
- If used too early, pain medication won't work later
- Injections are the best route for medication

## Pain is Common

- Pain is the most common complaint of the cancer patient
- Pain is not adequately controlled in up to 80% of cancer patients

## Pain Is a Major Public Health Issue

- 80% of patients present for health care because of pain
- Over 40% of acute care patients report poor pain control
- 26% of nursing home residents with daily cancer pain received NO pain medications

## Pain Is a Major Public Health Issue

- Minority patients, female, cognitively impaired, or older are significantly less likely to receive pain medication
- 50% of dying patients report moderate to severe pain
- Unrelieved pain costs our economy \$\$\$

## Why Do We Fail to Control Pain?

- The wrong attitude
  - what people believe about pain/opioids
- Lack of knowledge
  - What is pain? How to treat it
- Sub-optimal practices
  - failure to assess
  - failure to provide adequate pharmacotherapy
  - failure to use all available modalities

## Physician-Related Reasons for Inadequate Pain Management

- Survey of 1177 Oncologists:
  - Inadequate Pain Assessment (79%)
  - Patient Reluctance to Report Pain (62%)
  - Patient Reluctance to Take Opioids (62%)
  - MD Reluctance to Prescribe Opioids (61%)

## Physicians Anxiety About Managing Chronic Pain With Opioids

- Uncertainty related to assessment
- Concern about detrimental side effects
- Unfamiliarity with opioids, adjuvants
- Fear of addiction
- Fear of lawsuits
- Fear of regulatory scrutiny

## Patients' Reasons for Inadequate Pain Management

- Fear of addiction
- Fear of side effects
- Expectations are low
- Choice of treating disease or pain
- Fear of disappointing, annoying

## Physical Dependence

- “A physiologic state of neuro-adaptation which is characterized by the emergence of a withdrawal syndrome if drug use is stopped or decreased abruptly”
- Physical dependence is an expected result of opioid use
- Physical dependence, by itself, does not equate with addiction

## Tolerance

- A physiologic state resulting from regular use of a drug in which an increased dosage is needed to produce the same effect, or a reduced effect is seen with a constant dose
- May or may not be seen during opioid treatment and does not equate with addiction

## Addiction

- A neurobehavioral syndrome with genetic and environmental influences that results in physiological dependence on the use of substances for their psychic effects and is characterized by compulsive use despite harm

## Pseudoaddiction

- Pattern of drug-seeking behavior of pain patients who are receiving inadequate pain management that can be mistaken for addiction

## Behaviors More Predictive of Addiction

- Selling prescription drugs
- Prescription forgery
- Stealing or “borrowing” drugs from others
- Injecting oral or transdermal formulations
- Obtaining prescription drugs from non-medical sources
- Concurrent abuse of alcohol or illicit drugs
- Multiple episodes of Rx loss/other seeking

## Behaviors More Predictive of Addiction

- Evidence of deterioration of ability to function at work, with family, socially, that appears to be related to drug use
- Repeated resistance to changes in therapy despite evidence of adverse effects or psychological effects

## Behaviors Less Predictive of Addiction

- Aggressive complaining about the need for more drug
- Drug hoarding during periods of reduced symptoms
- Requesting specific drugs
- Openly acquiring similar drugs from other medical sources

## Behaviors To Watch For

- Wants end of office hour appointments or arrives just after close
- Needs immediate action – running late
- Not interested in PE or tests
- No permission for medical records
- Can't or won't name past providers
- Out of town, lost rx, stolen
- Allergies to non-opioids with no medical basis
- Unusual knowledge of controlled substances

## What is Pain?

- Whatever the patient says it is
- Both a physical and emotional experience
- “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

## Visceral Pain

- Arises from direct stimulation of afferent nerves of the soft tissue or viscera
  - often from tumor infiltration
  - also constipation, radiation, chemotherapy
- Tends to be poorly localized
- Difficult to define
- Can be deep, aching, or colicky
- Generally opioid responsive

## Somatic Pain

- Due to soft tissue inflammation or metastatic disease to the bone
- Usually well localized and “sharp”
- Typically constant and increases with movement
- NSAIDs are the mainstay of treatment
- Somatic pain is responsive to opioids

## Neuropathic Pain

- Due to neuronal injury
- May not be responsive to opioid therapy
- Patients may report pain due to sources that typically do not cause pain
- Described as burning or electrical
- Antidepressants or anticonvulsants are typical here

## Pain Assessment

- Comprehensive Assessment
  - Detailed histories
    - Pain/pain treatment
    - Medical
    - Psychosocial
  - Physical examination
  - Mental status assessment

## General Principles of Pain Assessment

- Intensity
- Location
- Aggravating/Relieving Factors
- Quality
- Timing
- Radiation
- Meaning
- WILDA

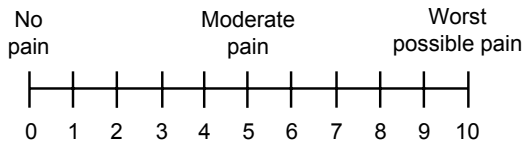
## Intensity

- Quantify pain
- Numeric rating scale is most common
- Visual analog scale/Verbal rating scale
- Objective evaluation of efficacy
- Ask if pain is interfering with daily activities

## Intensity (0-10)

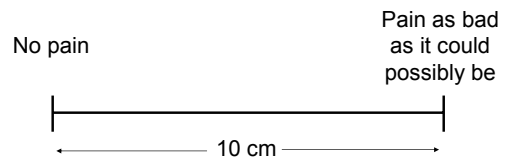
- Ask specific questions about the pain
  - 0 is no pain at all, 10 is the worst pain you can imagine
- What is your pain level now?
- What has the average been
  - over the last 5 days (chronic pain)?
  - over the last 24 hours (acute pain)?

## Numeric Pain Intensity Scale



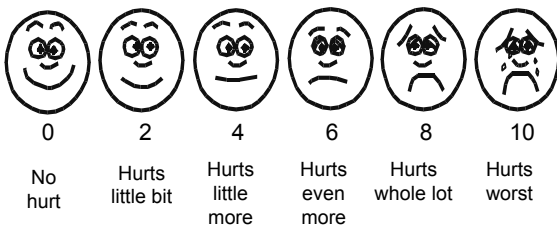
(AHCPR 1994)

## Visual Analogue Scale (VAS)



(AHCPR 1994)

## Wong-Baker FACES Pain Rating Scale



(From Wong DL, Hockenberry-Eaton M, Wilson D, et al. *Whaley & Wong's Nursing Care of Infants and Children*. 6th ed. St Louis, MO: Mosby-Year Book, Inc; 1999. © Mosby. Reprinted with permission.)

## Location

- Location can help determine the type and nature of the pain
- Pain may
  - be well localized without radiation
  - follow a dermatomal distribution
  - poorly localized and deep
- Body marking pens help demonstrate location

## Aggravating/relieving Factors

- Factors that aggravate or relieve may help in management
- Pain may
  - increase with movement
  - intensify with certain positioning
  - worsen with touching

## Quality

- Offer a list of adjectives to describe pain
- Descriptions include
  - sharp, aching, constant
  - burning, shooting, electrical, pins and needles
  - deep, colicky

## Words to Describe Pain

- |            |             |
|------------|-------------|
| ■ Burning  | ■ Cramping  |
| ■ Aching   | ■ Radiating |
| ■ Tender   | ■ Pressure  |
| ■ Shooting | ■ Throbbing |
| ■ Tingling | ■ Numbness  |

## Timing

- Identify timing of pain
- Intensification at certain times of the day may indicate a need for increased dose

## Radiation

- Does the pain radiate?
- The presence of radiation can help identify the pain type
- Radiation over dermatomal or nerve distributions can help localize the presence of a tumor

## Meaning of the Pain

- Understand how a patient may regard an increase in pain
- Patient's may be unable to rate pain
- Monitoring behavior is also key
  - mood swings, agitation, restlessness, increased fatigue

## How Does the Pain Affect?

- Sleep
- Appetite
- Energy
- Activity
- Relationships
- Mood

## Pain Assessment in the Elderly

- Poor memory, depression and sensory impairment may make getting pain information from the patient difficult
- Use of standard tools
- Pain assessment by proxy

## Assessing the Demented Patient

- Recognizing pain behaviors
  - facial grimacing
  - guarding any areas
  - change in breathing patterns
  - restless impatient motion
  - isolation, increasing time in bed / alone
  - negative vocalizations

## Assessing Pain in the Ventilated Patient

Modified Behavioral Pain Scale (for ventilated patients)		
ITEM	DESCRIPTION	SCORE
Facial expression	Relaxed	0
	Partially tightened (e.g., brow lowering)	1
	Fully tightened (e.g., eyelid closing)	2
	Grimacing	3
Upper limbs	No movement	0
	Partially bent	1
	Fully bent with finger flexion	2
	Permanently retracted	3
Compliance with ventilation	Tolerating movement	0
	Coughing but tolerating ventilation most of the time	1
	Fighting ventilator	2
	Unable to control ventilation	3
Vital signs	No change from baseline	0
	> 10% change from baseline	1
<b>TOTAL SCORE</b>		

## Assessing Pain in Infants and Children

- PIPP
  - Premature Infant Pain Profile
  - Less than 36 weeks
- CRIES
  - Neonatal Postoperative Pain Scale
  - Crying, Requires O2, Increased vital signs, Expression and Sleeplessness
  - Less than 1 year of age
- FLACC
  - Face, Legs, Activity, Cry Consolability
  - Children > 1 year of age

## Reassessment of Pain

- Routinely
  - 5th VS
  - q 2h, q 4h, q 8h
  - Weekly, monthly (chronic)
- After pharmacologic intervention
  - 30 min after IV
  - 60 min after PO
  - 24h after Transdermal

Characteristic	Acute Pain	Chronic Pain
Relief of pain	Highly desirable	Highly desirable
Dependence and tolerance	Unusual	Common
Psychological Component	Usually not present	Often a major problem
Organic cause	Common	Often not present
Insomnia	Unusual	Common
Treatment goal	Cure	Rehabilitation

## Pharmacotherapy of Pain

### WHO Pain Ladder

- Step 1 - Mild Pain
  - acetaminophen or NSAID ± adjuvant
- Step 2 - Mild to Moderate Pain
  - weaker opioid + APAP or NSAID ± adjuvant
- Step 3 - Moderate to Severe Pain
  - stronger opioid + APAP or NSAID ± adjuvant

### Step 1 Agents

- Aspirin
- Acetaminophen (APAP)
- Non-steroidal anti-inflammatory agents (NSAIDs)
- “Mild” opioids
- These agents have a “ceiling effect”
- Include in all pain regimens unless contraindicated

### Aspirin

- One of the oldest analgesics
- Inhibits platelet action permanently
- Most common adverse effects are gastric disturbances and bleeding
- Avoid in children under 12 years
- Associated with hypersensitivity reactions
- Usual dosage: 325-650mg Q4h

### Acetaminophen

- Useful for mild pain or fever
- Maximum daily dose is usually 4 grams
  - 2.5 g daily max. in those with 2 oz. daily EtOH
  - Hepatotoxic at therapeutic doses in chronic alcoholism or liver disease
- No risk of GI bleeding alone
- First choice for osteoarthritis of the hip and knee and renal disease
  - Don't be afraid of maximum dose 1000mg QID
- Usual dosage: 325-650mg Q4h

## NSAIDs

- Useful for mild pain and inflammation (acute or chronic)
- Reported adverse events higher than any other prescription class
  - GI intolerance most common (dyspepsia, abdominal pain and nausea)
  - renal
  - cardiovascular
- AE Profile often limits use

## NSAID Adverse Events

### *Gastrointestinal*

- Peptic ulcer development
- Risk factors
  - Age >65, h/o PUD or complications, high dose or multiple NSAID use, concomitant glucocorticoid or anticoagulant use, duration of therapy >3 months
- Ibuprofen and diclofenac least risk
- Naproxen, indomethacin, sulindac – moderate risk
- Ketoprofen, tolmetin, piroxicam – highest risk
- Risk minimized with H<sub>2</sub>'s, PPI's or misoprostil

## NSAID Adverse Events

### *Renal*

- Inhibit renal prostaglandins
- May exacerbate renal insufficiency
- Risk factors for acute nephrotoxicity
  - CHF, chronic renal insufficiency, cirrhosis, intravascular volume depletion, and diuretic therapy

## NSAID Adverse Events

### *Cardiovascular*

- Inhibit platelet aggregation
- May interact with antihypertensive therapy
- May increase blood pressure through inhibition of prostaglandins and fluid retention
  - Elderly are most susceptible
- Indomethacin and naproxen are most associated with large increases in BP

## COX-2 Inhibitor - Celecoxib

- COX-1 found in the GI
- COX-2 found in inflammatory tissue
- Similar efficacy as traditional NSAIDs
- Less GI side effects?, reduced risk of GI bleed?
- No less nephrotoxicity
- Sulfa moiety
- Associated with blood pressure elevations
- Associated with thrombosis???

## COX-2 Rofecoxib (Vioxx)

- September 30, 2004 rofecoxib voluntarily withdrawn from market
  - Increased risk of cardiovascular events
- “Trend toward increased cardiovascular risk” for all COX-2's but evidence hasn't been finalized
  - Evidence for Vioxx much stronger than others but there appears to be a clear mechanistic explanation that would apply across the class
  - FDA Advisory Committee Findings

## Ketorolac (Toradol®)

- Potent NSAID-IV, IM, PO
- Frequent and severe adverse reactions associated with recommended dosing
- Short term pain management ONLY (≤ 5 days)
  - 30 to 60mg IM or 30mg IV to start
  - 15 to 30mg IV or IM to follow q6h
- Initiate therapy with IV or IM ONLY
- PO as continuation of IV/IM therapy ONLY
- Age >65 years, renal impairment or weight <50kg require half standard dose

## Non Acetylated Salicylates

- May have fewer GI side effects than aspirin
- May not affect bleeding time
- May not affect platelet aggregation
- Include:
  - choline salicylate (Arthropan)
  - Diflunisal (Dolobid)
    - (platelets and bleeding time inhibited at higher doses)
  - magnesium salicylate (Doan's, Nuprin)
  - Choline magnesium trisalicylate (Trilisate)

## NSAID Selection

- Efficacy similar at equipotent doses
  - Patient response to specific agents may differ
  - Serial trials are recommended
- Differences in protein binding, metabolism, and active drug available can create interpatient variability
- Past response, cost, and dosing frequency, adverse effects and patient preference
- Note: in bone pain an NSAID must be added to the regimen (unless CI) for optimum relief

## “Mild” Opioids

- Propoxyphene and Codeine
- “Evidence does not support the use of propoxyphene in OA or RA pain. The use of codeine and propoxyphene should be avoided because of their side effects and limited analgesic effectiveness”

*American Pain Society*

## Propoxyphene (Darvon®)

- Propoxyphene alone same as placebo
- Propoxyphene plus acetaminophen no better than acetaminophen alone
- Toxic metabolites of propoxyphene may accumulate in renal/hepatic disease
- Side effects include twitching, tremors, sedation and seizures
- Has been associated with a 60% increase in risk of hip fracture in the elderly

## Codeine

- Considered a mild analgesic
- 30mg alone is less analgesia than 650mg acetaminophen or aspirin
- Codeine alone is no more effective than placebo in OA pain
- Codeine plus NSAID only slightly more effective than NSAID alone

## Codeine

- Very constipating
- Effective for moderate pain when combined with acetaminophen or aspirin
- 30 to 60mg to start
- 10 to 30 minute onset, 4 to 6 hour duration
- Undergoes hepatic metabolism
  - ~10% is metabolized to morphine

## Choice of Step 1 Agent

- Consider patient
  - Clotting disorder?
  - H/o PUD?
- In renal disease avoid any salicylate or NSAID
- In salicylate or NSAID allergy use APAP
- Recent history of GI bleed (within 3 months), misoprostil is protective as are PPI's or H2's

## Step 2 Agents

- Most of these agents are in combination with APAP greatly limiting their use
- Ex: Lorcet, Lortab, Vicodin, Percocet, Percodan

## Codeine Combinations

- Acetaminophen 120mg with codeine 12mg in suspension, solution, and elixir
- Acetaminophen 300mg with codeine 15mg, 30mg and 60mg tablets (Tylenol #2, #3, #4)
- Aspirin 325mg with codeine 30mg (Fiorinal) and 60mg

## Hydrocodone

- Very effective for moderate pain when used in combination with APAP or ibuprofen
- Less constipation than codeine at equianalgesic doses
- Patients able to tolerate maximal doses
- 4 to 6 hour duration
- Vicoprofen, Lortab, Vicodin, Lorcet

## Oxycodone in Combination (Percodan, Percocet, Tylox)

- Typically in combination with acetaminophen
- Doses limited by the amount of acetaminophen
- 15 to 30 minute onset, 4 to 6 hour duration
- Available alone as immediate release or controlled release Oxycontin (q12h)

### Step 3 Agents

- Morphine is the standard by which all other opioids are compared
- The side effect profiles of opioids are basically the same - minor differences in confusion, constipation and possibly sedation
- A given patient will respond slightly differently to any individual opioid

### Opioid Routes of Administration

- Oral
- Buccal
- Sublingual
- Intranasal
- Aerosolized
- Rectal
- Transdermal
- Transmucosal
- SC (bolus or infusion)
- IV bolus
- IV PCA
- Epidural
- Intrathecal
- Spinal

### Opioid Analgesics

- Cornerstone of pain control
- Bind to specific opioid receptors in the brain, spinal cord and GI tract
- Bowel regimens should accompany their use
- Transient side effects include nausea/vomiting or sedation
- Frequent assessment is required
- Can be NSAID sparing

### Opioid Adverse Effects

- Respiratory depression
- Sedation
- Nausea
- Dizziness
- Constipation
- Pruritis

### Anticipate Adverse Effects

- Respiratory depression
  - Pain is a potent respiratory stimulant
  - Beware in opioid naive
  - Rare in patients receiving chronic opioid therapy
  - Patients do not succumb to respiratory depression while awake

### If Respiratory Depression Occurs

- Establish airway, supply oxygen and ventilate if necessary
- Naloxone 0.4mg in 9mL saline, given as 0.5mL slow IV push q2 minutes
- Repeated dosing may be necessary
- Careful titration required

## Anticipate Adverse Effects

- Sedation
  - May be counteracted with stimulant agents
    - Caffeine
    - Dextroamphetamine
    - Methylphenidate
- Nausea and dizziness
  - Change the regimen or route to avoid high serum peak levels
  - Add antiemetics

## Anticipate Treat Adverse Effects

- Constipation
  - Use a bowel regimen of **stimulant** agent +/- stool softener
  - Change route to minimize concentrations at the affected site
- Pruritis
  - Fentanyl and oxymorphone have less propensity for histamine release
  - Add an antihistamine

## Options for Treatment of Adverse Effects

- Change regimen or route of current agent
- Try a different opioid
- Add an agent to treat effect
- Alter the route to avoid site specific effects

## Considerations for Step 3 Agents

- Begin with least invasive route and progress
- Include patient choice and autonomy
- Start with IR formulation, titrate to pain relief and switch to long acting agent
- All long acting regimens must have a short acting agent for breakthrough pain
- Administer appropriate agents to prevent side effects (antiemetics/laxatives)
- Warn patient/family of adjustment period

## Strong Opioids

### Short Acting

- Morphine
- Hydromorphone
- Oxycodone
- Fentanyl
- Meperidine

### Long Acting

- Fentanyl topical
- Methadone
- Morphine SR
- Oxycodone SR

## Morphine

- GOLD STANDARD
- 4 hour duration of action for immediate release formulations
- 15 to 30mg PO to start
- Sustained release formulations offer 8-12 (MS Contin) or 24 hour dosing (Kadian)
- Metabolite M6G is more potent
  - Accumulation can occur in renal dysfunction

## Hydromorphone

- First alternative to morphine
- More potent, better soluble than morphine
- Slightly shorter duration than morphine
- Inactive metabolites
- 4 to 8mg to start
- 15 to 30 minute onset, 3 to 4 hour duration

## Oxycodone

- Extensively metabolized
  - Noroxycodone- major metabolite, weaker analgesic
  - Oxymorphone – minor metabolite via CYP2D6
- Immediate release
  - 15 to 30 minute onset, 3 to 4 hour duration
  - Start at 5-15mg q 3-4 hours
- Controlled release (12 hour duration)
  - 10, 20, 40 and 80mg tablets
  - Do not break, crush, chew

## Fentanyl

- 7+ hour half-life
- Onset and duration of analgesia depends on administration route
  - IV: rapid onset, 30-60 minute duration
  - Topical: several hour onset, 48-72 hour duration
  - Actiq: 5-15 minute onset, at least one hour duration; varies

## Fentanyl Analgesia Indications

- IV
  - Chronic and acute
  - Preoperative and interoperative
- Transdermal
  - Chronic, malignant and non-malignant
- Actiq
  - Breakthrough pain in opioid tolerant patients with malignant pain

## Transdermal Administration (Duragesic)

- Approved for chronic pain
- Theoretically less constipating
- Use short acting opioids first to titrate to pain relief then for breakthrough pain
  - 12-16 hours to achieve therapeutic effect
  - 48 hours to reach steady state
- Package insert:
  - 25mcg/hr patch = 30mg MS q8h
  - Very conservative

## Oral Transmucosal fentanyl citrate (OTFC)

- Solid dosage form of fentanyl in a sweetened lozenge on a stick (Actiq)
- Approved for breakthrough pain in cancer patients
- Instruct patient
  - **RUB** on mucosal tissue
- Takes 15 minutes to consume, then 5 to 10 minutes to peak

## Meperidine

- Most over-used and under-dosed agent
- Three hour duration at most
- 10 - 45 minute onset
- Toxic metabolite, nor-meperidine, accumulates to cause anxiety, agitation, tremors and seizures (15 to 30 hour  $t_{1/2}$ )
- 50mg orally provides less analgesia than 650mg acetaminophen
- 75mg IV to start; avoid oral use
- Offers no benefit in pancreatitis or sickle cell disease

## Methadone

- Very long half-life
  - 22 hours in young, healthy volunteers
  - 60-70 hours in the elderly or hepatic impairment
- 5 to 10mg to start
- Slow onset (30 to 60 minutes)
- Decrease doses by 25% weekly after optimal analgesia achieved

## Mixed Agonist-antagonists

(pentazocine, nalbuphine and butorphanol)

- Analgesic and respiratory depression effects are less than morphine like agonists
- No real advantage over morphine like agonists
- Side effects
  - Confusion and hallucinations
  - Opioid withdrawal
- All have ceiling effect
- Not first line

## Tramadol

- Effective for moderate pain
- Can be dose sparing for NSAIDs
- Start at 50mg q4-6h and titrate slowly up to 400mg /day
  - SLOW titration reduces side effect potential
    - Nausea, vomiting and dysphoria
  - Use 12 hour interval in renal impairment
    - $Cl_{cr} < 30\text{ml/min}$ , 200mg/d maximum

## Use of Opioids

- Frequently assess pain and response to tx
- Communicate
- Anticipate side effects and be proactive
- Never abruptly stop
- Around the clock medication
- Determine correct dose by relief of pain
- No ceiling exists in opioid dosing
- Use adjuvant therapy when appropriate

## Why Not Standard Morphine....?

- Favorable experience with another drug
- Want longer duration of action
- Avoiding adverse effects
- As tolerance develops
- Need more rapid onset
- Alternate dosage form

## Individualizing Pain Therapy

- Choose a route, dose and schedule
  - Optimal analgesic doses will vary widely among patients
  - Give each analgesic an adequate trial
- Administer analgesics regularly (& prn)
- Know the regimens of several strong opioids

## WHO Recommendations for Drug Therapy

- By the Mouth
- By the Clock
- By the ladder
- For the individual
- With attention to detail

## Starting Opioid Therapy

- Use ATC for persistent pain
- Use PRN for episodic pain
- Remember to assess frequently
  - Increase dosing based on pain level
  - 25% increase for slight pain
  - 50% for moderate pain
  - 100% for severe pain

## Equianalgesic Dosing

- An ESTIMATE!!!
- Individualize and titrate dose to patient response and situation
- Use equianalgesic dosing references as *guidelines*

## Equianalgesic Dosing

Opioid	Equianalgesic Dose	Dose Interval
Morphine	PO: 30mg IV: 10mg PR: 30mg	2-4 hours
Hydromorphone	PO: 7.5mg IV: 1.5mg PR: 7.5mg	3-4 hours
Oxycodone	PO: 20-30mg	3-4 hours
Fentanyl	IV: 100mcg OTFC: unknown	30-60 min
Hydrocodone	PO: 30mg	3-4 hours
Meperidine	PO: not advised IV: 75mg	2-3 hours
Morphine SR	PO: 30mg	8-12 hours
Oxycodone	PO: 20mg	8-12 hours
Fentanyl	TD: 20mcg	72 hours
Methadone	PO: 2-8mg IV: 1-4mg	PO: 6-8 hrs IV: 4-8 hrs.

## Opioid Conversions

- Incomplete cross-tolerance
  - When switching from one opioid to another, decrease dose by 25%
  - May not be necessary if pain is not well controlled on original agent

## Conversion Example

- JB has pain well controlled by 6 tabs Percocet-5mg/24 hours
  - Wants to change to long acting agent
  - MS Contin
- 6 Percocet-5 = 30mg oxycodone/24 hr
  - 5mg oxycodone x 6 tabs/day = 30mg
- Check conversion chart
  - Oxycodone 20mg = morphine 30mg

## Percocet to MS Contin cont.

- Set up ratio equation
  - $\frac{30\text{mg oxycodone}}{20\text{mg oxycodone}} = \frac{x \text{ mg morphine}}{30\text{mg morphine}}$
  - $900\text{mg} = 20x \quad x = 45\text{mg morphine}$
  - Reduce by 25% since well controlled pain
  - $45\text{mg} \times .75 = 33.75\text{mg} = 15\text{mg MS Contin q12h}$

## Another Method

- Total 24 hr dose of current drug = 30mg
- Equianalgesic dose of current drug = 20mg
- Divide 24 hr total by equianalgesic dose
  - $30\text{mg}/20\text{mg} = \text{equianalgesic dosing units}$
  - 1.5
- Equianalgesic dose of new drug is 30mg (morphine)
- Multiply new drug by equianalgesic dosing units of current drug
  - $30\text{mg} \times 1.5 = 45\text{mg}$  (24 hr dose of morphine)
- Reduce dose by 25%
  - $45\text{mg} \times 0.75 = 33.75\text{mg/day}$
- Divide by 2 (12 hr dosing) = 16.875
  - New dose = 15mg MS Contin q12h

## New Problem

(Convert IV meperidine to MS Contin)

- Patient is on IV meperidine 50mg IV q4h for hip pain that is not well controlled. Physician wants to convert to long-acting PO morphine
- 24 hr dose of meperidine = 300mg
- $\frac{300\text{mg meperidine}}{75\text{mg}} = \frac{x \text{ mg morphine}}{30\text{mg}}$
- $900 = 75x \quad x = 120\text{mg morphine}$
- Divide 120mg by 2 for q12h product
- New Dose = 60mg MS Contin po q12h

## Fentanyl Transdermal Conversions

- To dose Duragesic patches
  - Calculate the total 24 hr oral morphine equivalent and divide by 2, then apply closest patch size
- Patient feeling pain despite 2mg MS/hr IV
  - Morphine 2mg/hr = 48mg/day IV
  - $48\text{mg}/10\text{mg IV} = x \text{ mg} / 30\text{mg po}$
  - $X = 144\text{mg po morphine}$
  - Divide by 2 = 72mg so use 75mcg patch/q 72 hrs
  - Dose not reduced since pain not well controlled

## Fentanyl Transdermal Conversions

- Patient taking MS Contin 60mg q12h and used 4 doses 15mg MSIR for breakthrough
  - Calculate total daily morphine dose
    - $120\text{mg} + 60\text{mg} = 180\text{mg po morphine}$
    - Divide by 2 = 90mg
  - If comfortable then use
    - 75mcg patch
  - If not comfortable, then use
    - 100mcg patch

## Methadone Conversions

- A bit tricky to convert
- Incomplete cross tolerance
  - Increases with increased morphine dose/equivalent
    - 0-90mg MS – 4:1
    - 90-300mg MS – 8:1
    - 300-600mg MS – 12:1
    - 600-1000mg MS – 15:1
    - >1000mg MS – 20:1

## Conversion Example

- Patient is receiving 60mg MS Contin BID
  - Pain is not well controlled
- 120mg MS / day so use 8:1 ratio
  - 15mg methadone
  - Use 5mg tid
- Continue with breakthrough opioid

## Breakthrough Pain

- For all patients on long acting opioids
- Typically an immediate release (IR) opioid given q2h
- Frequently use breakthrough pain requirements to assess need for titration
- Add breakthrough requirements over 24hrs, then add this number to total of long acting agent
- If patient required >2 breakthrough doses in 24 hours then an increase in basal agent is required

## Breakthrough Dosing Example

- SD is taking MS Contin 30mg po q12h
  - 60mg morphine/ 24 hours
- Breakthrough dose is 10-20% of total daily dose
  - 6-12 mg po morphine
  - q2h prn
- SD should receive 5-10mg po/sl morphine (IR) product q2h as needed

## Pharmacotherapy of Neuropathic Pain

## Neuropathic Pain

- No real tools in determining drug selection
- Description of pain is often the first step
- Trial and error
- Start at the lowest possible dose and titrate slowly to pain relief, intolerable side effects or therapeutic range
- Titrate only 1 drug at a time

### Tricyclic Antidepressants

- First line for all types of neuropathic pain except trigeminal neuralgia
- Amitriptyline has the best efficacy but the worst side effects (anticholinergic)
  - 25mg starting dose up to 150mg/d qhs
- Nortriptyline or desipramine often preferred
  - Dose during the day due to possible insomnia
- Often considered best for *constant burning* type pain

### SSRI's

- Neuropathic pain or pain complicated by depression or insomnia
- Not as effective as TCA's
  - generally reserve for those who fail TCA's
- Paroxetine starting at 20mg qd
  - Daily dose: 20-40mg

### Gabapentin

- Quickly becoming first line
  - As effective as TCA's
- Much lower incidence of side effects than carbamazepine and phenytoin
  - Somnolence, dizziness, weight gain, dry mouth
  - Does not require monitoring of CBC or LFT's
  - No major drug interactions
- Usual starting dose is 100mg QD titrating slowly to TID
  - Generally 900 to 3600mg/d

### Anticonvulsants

- Considered second line agents for neuropathic pain
- Often preferred for *lancinating or stabbing* type pain
- Carbamazepine – effective but limited by side effects, lab monitoring
  - Start at 300mg/d qhs
- Phenytoin – less effective than carbamazepine
  - Requires CBC and LFT monitoring
  - q8h, start 500mg; 750-2250mg/d
- Valproate – side effects limit use

### Clonidine

- Recent approval of clonidine via epidural infusion for the treatment of pain
  - Indicated for the treatment of severe pain that is not adequately controlled by opioids alone
  - Start at 30mcg/hr
- Effective especially for neuropathic pain
- Hypotension and bradycardia possible side effects

### Local Anesthetics

- Used extensively for acute pain management
- Topical Lidocaine 5% patch
  - Lidoderm
  - Approved for post-herpetic neuralgia
  - Worn 12 hrs on 12 hrs off
  - May be cut to size; up to 3 patches a day

## Skeletal Muscle Relaxants

- May be useful as acute adjunct for muscle injury
  - Benzodiazepines, sedatives, antihistamines
  - Risk of dependence

## Capsaicin

- Depletes substance P from neurons
- Most useful as adjunct vs. monotherapy
- 0.25% to 0.75% cream
  - Apply tid to qid
  - Requires several weeks for efficacy
- Local burning initially

## Pregabalin (Lyrica)

- New agent for Diabetic Neuropathy and Postherpetic Neuralgia
  - 150 to 600mg/day
  - Renal dosage adjustment
  - Most frequent adverse effects
    - Dizziness, drowsiness, peripheral edema
  - Pain relief reported as early as the first week, sustained over 3 months

## Adjuvant Use Principles

- Avoid polypharmacy initially
- Choose agents with best side effect profile
- Start low and titrate slowly
- Try different agents within the same class

## Adjuvant Agent Principles

- Patient Education
  - Efficacy may be delayed
  - Will not provide full pain relief
  - Trial and Error
  - Side effects especially in first week
  - Tolerance to side effects common

## Adjuvant Agent Principles

- Continue therapy long term if:
  - Pain relief  $\geq$  50%
  - Documented improvement
  - Side effects tolerable/manageable