

PAIN MANAGEMENT

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OBJECTIVE



WHAT HAS BEEN YOUR TOUGHEST PAIN CASE???



- Write down what the circumstances surrounding the case
- Write down what was done
- Tell us what worked and what did not work
- Tell us what frustrated you about this case and if anything about it was rewarding

THE PROBLEM

- 50 million Americans disabled secondary to pain
- Morbidity secondary to pain twofold greater in patients over 60.
- Seen in 40-85% of patients in long term care facilities
- One month before death, 66% report pain frequently or all the time
- In Michigan pain study
 - 70% of chronic pain patients have pain despite treatment
 - 22% stated treatment worsened pain
- 74% of trauma patients judged to have inadequate analgesia based on pain intensity scores

PAIN IN AMERICA

- Phone survey-Hart Research Associates July 2003 (1,004 adults)
- 76% personally/family member/friend suffer from chronic pain-57% personally
- Pain types
 - Back pain – 28%
 - arthritis/joint pain – 19%
 - Headaches/migraines – 17%
 - Knee pain – 17%
 - Shoulder pain 7%
- Every age group affected
 - 18-34 – 54%
 - 35-49 – 56%
 - 50-64 – 63%
 - 65+ – 57%



PAIN IN AMERICA

- 75% make life-style adjustments
 - 20% Disability from work, 17% change jobs, 13% help with daily living, 13% move to another home
- 90% did seek professional help
 - Rx 69% (58% effective)
 - Chiropractic Tx (54% effective)
 - Surgery 32% (54% effective)
 - Physical therapy 48% (48% effective)
 - OTC medications 79% (41% effective)
 - Other Tx 20% (40% effective)
- 72% physicians supportive, 51% of bosses supportive
- 57% would be willing to pay an extra \$1.00 a week in taxes to pay for more pain research



CLINICAL CONSEQUENCES OF PAIN

- Depression
- Decreased socialization
- Sleep disturbances
- Impaired ambulation
- Increased health care costs
- Pulmonary dysfunction
- Decreased ambulation
- Gastrointestinal complications
- Decreased quality of life



DEFINITION OF PAIN



Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

ALTERNATIVE DEFINITION OF PAIN

Pain is whatever the patient says/feels it is, existing whenever he or she says/indicates it does.



TYPES OF PAIN

- ACUTE
 - Follows injury
 - Generally disappears when injury heals
 - Well-defined temporal onset
- CHRONIC
 - Persists beyond expected healing time
 - Cause may be hard to define
- CANCER
 - Definable cause
 - Can be acute, recurrent, or chronic



LABELS MAKE A DIFFERENCE

- The terms “chronic” and “persistent” pain used interchangeably
- In older persons (younger?) “chronic” label can conjure up negative images (psychiatric problems, futility in treatment, malingering, drug seeking behavior)
- The term “Persistent Pain” now officially has replaced “Chronic Pain” in all American Geriatrics Society Recommendations



CHRONIC/PERSISTENT PAIN

- Pain persisting beyond normal time for disease or healing
 - Sympathetically maintained pain
 - Myofascial pain
- Pain related to chronic degenerative disease or a persistent neurologic condition
 - Arthritis
 - Low back pain
 - Headache
 - Neuropathic
- Pain without identifiable cause
 - Fibromyalgia
 - Idiopathic ?

CHARACTERISTICS OF ACUTE AND CHRONIC/PERSISTENT PAIN

CHARACTERISTICS	ACUTE PAIN	CHRONIC/PERSISTENT PAIN
Relief of Pain	Highly Desirable	Highly Desirable
Dependence & Tolerance	Unusual	Common
Physiological Component	Usually Not Present	Often a Problem
Organic Cause	Common	Often Not Present
Family & Environment Involvement	Small	Significant
Sleep Problems	Unusual	Common
Treatment Goal	Cure	Rehabilitation & Acceptance

TYPES OF ONCOLOGY PAIN

- Acute
- Chronic/Persistent
- Pre-existing chronic/persistent pain + cancer pain
- Drug abuse + cancer pain
- Dying + cancer pain

IF WE CANNOT ASSESS PAIN, WE WILL
NEVER BE ABLE TO RELIEVE PAIN.

Betty R. Ferrell, Ph.D.

ASSESSMENT OF PAIN

- Careful history
 - Believe the patient and family
 - Assess the nature of the pain
 - Acute pain
 - Distinct onset, short duration, physical signs
 - Chronic/Persistent pain
 - Long duration, long-standing functional impairment
 - Consider neuropathic pain



ASSESSMENT OF PAIN

- CONSIDER ONSET, WHAT MAKES PAIN BETTER OR WORSE, LOCATION, DESCRIPTION, SEVERITY, AND DOES PAIN MOVE?
- Consider multiple pain types and/or sites.
- Assess psychosocial status
 - Emotional, Social, Cultural
- Assess functional status.



MEDICATION HISTORY

- All medications used in the past six months
 - Dose
 - Duration of use
 - Frequency of use
 - Reason for use
 - Perception of efficacy
- Social drug use (Do not forget alcohol)
- What worked, how well they worked, what did not
- Side effects
- Allergies
- Nonprescription drug use
- Nutritional supplements
- Alternative therapies



PAIN TREATMENT PLAN DEVELOPMENT

- Develop treatment plans using assessment tools and, whenever possible, include patient and family input.
- Remember in chronic pain it is unrealistic in most cases to expect COMPLETE relief of pain.
- Do systematic and ongoing reassessments with functional end points in mind.
- Change the plan as needed.
- Document the plan and all changes.
- The process should never end.

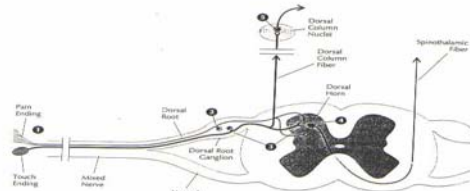


NOCICEPTION

- Nociceptors
 - On C-fibers and A-delta fibers
- Nociceptor activation
 - Noxious stimuli, bradykinins, histamine, inflammation, prostaglandins (sensitize receptors)
 - Depolarization of neuron
 - Substance-P is released and mediates neuronal inflammation
 - Nerve growth factor also is released with inflammation

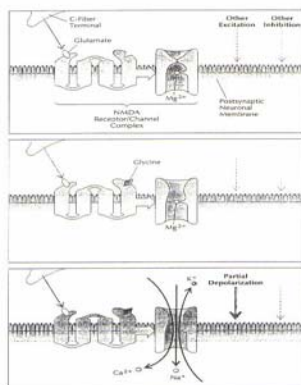
NEURONAL ACTIVITY

ref #3



EXCITATORY DORSAL HORN ACTIVITY

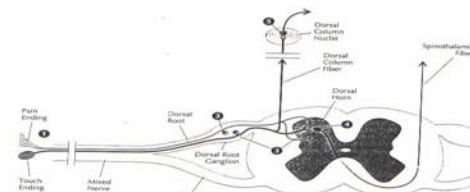
- Release of Substance P
- Release of glutamate
- Release of aspartate
- Excitatory Amino Acid Receptors (eg. NMDA)
- Central neuronal depolarization
- Pain signal sent to brain via spinothalamic tract



ref #5

NEURONAL ACTIVITY

ref #3



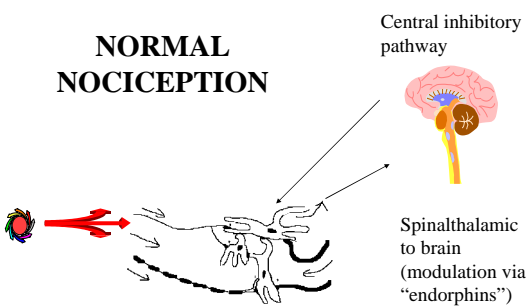
INHIBITORY DORSAL HORN ACTIVITY

- Glycine
- GABA
- Serotonin
- Norepinephrine
- Opioid receptors (endorphins)
- Stimulation of large afferent neurons (TENS)

ADAPTIVE INFLAMMATION

- Shift from prevention of injury to promotion of healing
- Injured area becomes more sensitive to pain due to inflammatory process
- Increased responsiveness of neurons within CNS
- Decreases movement and contact with injured area

NORMAL NOCICEPTION



PAIN=SUMMATION OF EXCITATORY AND INHIBITORY FACTORS

PAIN MANAGEMENT PHARMACOLOGY= MANIPULATION OF PAIN PATHWAY

NOCICEPTIVE PAIN AND PHARMACOLOGY

- Acetaminophen/NSAIDs/ASA--central and peripheral prostaglandin inhibition
- Opioids--affinity for CNS opioid receptors
 - NOTE effect not only presynaptic release of substance P in the dorsal horn but also on opioid receptors in the brainstem and midbrain exacerbating inhibitory modulation



NEURONAL PLASTICITY

- Nerve damage or extended/constant/intense bombardment of nociceptive pain fibers
 - Abnormal activity or distribution of voltage-gated sodium channel
 - they fire spontaneously or continuously rather than only when stimulated
 - NMDA receptors (voltage sensitive) activated
 - changes in neuron (hard wire changes)
 - Sprouting of sympathetic fibers from normal targets (blood vessels) to pain fiber cell bodies
 - Sprouting of presynaptic non-pain nerve fibers into what is normally pain fiber areas of the dorsal horn

NEURONAL PLASTICITY

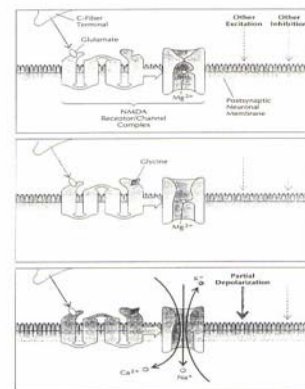
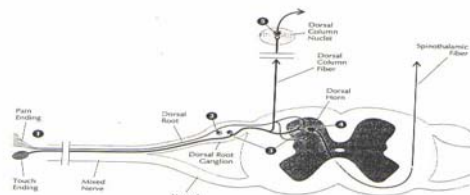
- Nerve damage or extended/constant/intense bombardment of nociceptive pain fibers
 - change in the neurotransmitters and neuroreceptors
 - Decreased substance P production in pain fibers
 - Increased substance P production in non-pain fibers
 - Change in/loss of the opioid receptors
 - Change in NMDA receptor may inhibit opioid receptor

NEURONAL PLASTICITY

- Nerve damage or extended/constant/intense bombardment of nociceptive pain fibers
 - CNS circuits accustomed to one set of signals are receiving another
 - Imbalance of excitation over inhibition (loss of descending inhibition)
 - Neuropathic pain (nerve damage) and functional pain (abnormal operation of nervous system)

NEURONAL ACTIVITY

ref #3



ref #5

NEURONAL PLASTICITY

- Abnormal pain generator and a reorganized receiver (connections, neurotransmitters, and receptors)
 - Helps explain abnormal sensation



ABNORMAL SENSATIONS

(ref #2-4)

- Spontaneous pain (paroxysmal or constant)
 - burning, shooting, lancinating
- Hyperalgesia
 - exaggerated painful response to a normally noxious stimulus
- Allodynia
 - painful response to a normally non-noxious stimulus (light touch–burning)



NEURONAL PLASTICITY

- Abnormal pain generator and a reorganized receiver (connections, neurotransmitters, and receptors)
 - Helps better explain why so called non-analgesics are helpful in some painful conditions



NON-OPIOID ANALGESICS

- Acetaminophen, aspirin, NSAIDs
- Affect prostaglandins
- Best for mild to moderate pain
- Results are poor when used alone for severe pain
- Perceptions often determine outcome
- Choice depends on cost, side effects, pharmacokinetics, and availability

ACETAMINOPHEN

- Most often prescribed analgesic in nursing facilities
- Analgesic and antipyretic
- Very little anti-inflammatory action
- Low cost and can be used in aspirin allergy
- JAGS--drug of choice for mild to moderate musculoskeletal pain
- As effective as ibuprofen in osteoarthritis
 - rheumatoid arthritis ?

ACETAMINOPHEN

- Optimal dose
 - 2.6-4.0 grams qd
 - some titration may be necessary
 - WHAT IS MAX DOSE PER DAY?????
 - Start at low doses and carefully monitor
 - No change in hepatic clearance in healthy elderly
 - Dosage reduction may be warranted in FRAIL elderly
- Well tolerated
 - > ? grams a day (increase in ALT in 39% of 106 healthy volunteers who took 4gm a day for 14 days)
 - Watch combination products and OTC use

ASPIRIN AND ASPIRIN-LIKE COMPOUNDS

- Analgesic, antipyretic, anti-inflammatory, and platelet inhibitor
- Low cost
- Side effects
 - GI
- Salicylate salts (non-acetylated)
 - Fewer GI effects
 - Less platelet inhibition
- Use caution in influenza



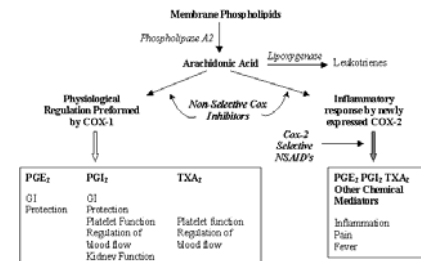
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

- Effective analgesic and anti-inflammatory
 - Difference in efficacy between drugs not well documented.
 - Considerable variability in patient response, so after reaching ceiling dose, switching to another drug is reasonable.
- 30 million people worldwide take daily
 - 40% > 60 years old
 - OTC-ibuprofen, naproxen, ketoprofen
- One of the drugs most frequently associated with ADRs in the world
 - 25% in United Kingdom



NSAID ADVERSE EFFECTS

- Gastrointestinal complications
 - 75,000 hospitalizations in US per year
 - 7,500 **DEATHS** per year
 - In elderly, the relative risk of PUD increases from 2.8 - 8.0 in those taking NSAIDs
 - 29% of PUD--NSAID induced
- Many life-threatening events asymptomatic
 - 58% of patients noticed no symptoms until acute event
- Lower GI tract may also be at risk



www.uic.edu/Lab/mesecar/exam_Review.htm

NSAID ADVERSE EFFECTS

- Recent research has shown at least two isoforms of the prostaglandin cyclooxygenase (COX 1 and COX 2).
 - It is hypothesized that by selectively inhibiting COX 2, you can get analgesia and anti-inflammatory effects without the GI side effects.
 - On the market
 - Celecoxib (Celebrex- Searle) Jan 99
 - Rofecoxib (Vioxx-Merck) June 99 (OFF MARKET Sept 2004)
 - Meloxicam (Mobic-BI) –NOT granted status of COX-2 inhibitor by FDA but has more selectivity than naproxen
 - Valdecoxib (Bextra- Pharmacia) Nov 2001 – OFF MARKET 2005)
 - Coming to market ?
 - Parecoxib (injectable prodrug of valdecoxib)
 - Etoricoxib (Arcoxia-Merk) more COX-2 selective
 - Lumiracoxib (Prexige-Novartis)

RISK OF CARDIOVASCULAR EVENTS ASSOCIATED WITH SELECTIVE COX-2 INHIBITORS ?

- COX-2 agents may tip the balance in favor of prothrombotic events
 - Nonselective NSAID's inhibit the production of prothrombotic thromboxane A2 and antithrombotic prostacyclin--Cox-2's have been shown to decrease prostacyclin without affecting thromboxane A2, thus it was hypothesized that COX-2 inhibitors may increase cardiovascular events

Mukherjee D, et al. Risk of cardiovascular events associated with selective Cox-2 Inhibitors. JAMA 2001;286(8):P954-959.

RISK OF CARDIOVASCULAR EVENTS ASSOCIATED WITH SELECTIVE COX-2 INHIBITORS ?

- Thus retrospective analysis of coxib studies preformed
 - Annualized MI rates higher for both celecoxib and rofecoxib than those in placebo groups in primary prevention trials of aspirin
 - In the celecoxib trial no significant difference in CV events with the NSAID's used in trial
 - In the rofecoxib trial there was a significant difference in CV events

Mukherjee D, et al. Risk of cardiovascular events associated with selective Cox-2 Inhibitors. JAMA 2001;286(8):P954-959.

VIOXX GASTROINTESTINAL OUTCOMES RESEARCH TRIAL (VIGOR)

- Randomized double blinded, comparing rofecoxib 50mg daily to naproxen 500mg BID
- 8076 rheumatoid arthritis pts (mean 58 yo)
- Median length of therapy 9 months
- No recent MI, Stroke, ASA
- Serious GI events 2%-rofecoxib, 4% naproxen
- Serious cardiovascular events (n=45-rofecoxib) (n=19-naproxen)** (significant difference)
 - Possible cardioprotection of naproxen?

RISK OF CARDIOVASCULAR EVENTS ASSOCIATED WITH SELECTIVE COX-2 INHIBITORS ?

- Conclusions?
 - Differences in the celecoxib and rofecoxib studies (dose, RA vs Osteo, Naproxen vs other NSAID, differences in study patients) lead several researchers to the conclusion that if this increase in CV effect is real, it is probably a class effect not a rofecoxib effect
 - COX-2 inhibitors may offer decreased potential for GI bleeding in patients who are at risk when compared to non-selective NSAID

Mukherjee D, et al. Risk of cardiovascular events associated with selective Cox-2 Inhibitors. JAMA 2001;286(8):P954-959.

ADENOMATOUS POLYP PREVENTION OF VIOXX (APPROVe) study

- Randomized double blinded, designed to evaluate efficacy of 25mg of rofecoxib daily versus placebo in preventing colorectal polyps in 2,600 patients with a history of colorectal adenomas
- Increased risk began 18 months after treatment (safety board did not stop after 1st 18 months)
- After 3 years the cumulative incidence of significant cardiovascular events was 7.5 per 1000 patients receiving placebo versus 16 per 1000 patients receiving rofecoxib
- Vioxx taken pulled from market by Merck September 30, 2004

Cardiovascular Safety of Celecoxib (Celebrex) and Valdecoxib (Bextra)?

- 3 Post hoc studies (Solomon DH, et al. Circulation. 2004;109:2068-2073, White WB et al. AM J Cardiol 2003;92:411-418, White WB et al. Am J Cardiol 2002;89: 425-4300) have shown no significant cardiovascular risk with celecoxib
- 1 Post hoc study (White WB et al. American Journal of Therapeutics 2004;11:244-250) has shown no significant cardiovascular risk with valdecoxib
- Celecoxib Long Term Arthritis Study (Class) did not show significantly increased rate of myocardial infarction with celecoxib compared to ibuprofen or diclofenac
 - A "retrospective approach to the data (those not receiving aspirin) also reveals signs of increased cardiovascular risk" FitzGerald GA. NEJM 2004;351:17, 1709.

Cardiovascular Safety of Celecoxib (Celebrex) and Valdecoxib (Bextra)?

- "We now have clear evidence of an increase in cardiovascular risk that revealed itself in a manner consistent with a mechanistic explanation that extends to all coxibs" (FitzGerald GA. NEJM 2004;351:17, 1709.)
- "the US regulatory agency has been remiss in not requiring coxib manufactures to undertake dedicated trials in patients with established cardiovascular disease" (Topel EJ. Lancet 2004;364:640)
- "it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents"(coxibs) (Topel EJ. NEJM 2004;351:1707.)

Cardiovascular Safety of Celecoxib (Celebrex) and Valdecoxib (Bextra)?

- "it is hard to imagine the justification for this extraordinary adoption of coxibs in light of of marginal efficacy, heightened risk, and excessive cost compared with traditional NSAIDs" (Topel EJ. Lancet 2004;364:640)
- "Selective inhibitors of COX-2 remain a rational choice for patients at a low cardiovascular risk who have had serious gastrointestinal events, especially while taking traditional NSAIDs." (FitzGerald GA. NEJM 2004;351:17, 1709.)

Treatment with ibuprofen in patients with increased risk of cardiovascular problems may limit the cardio protective effect of aspirin

- Aspirin was given before and after ibuprofen, acetaminophen, rofecoxib, diclofenac
- Platelet aggregation and thromboxane B(2) was measured on day 6 of administration and 24 hour after aspirin was given
- Aspirin induced inhibition of platelet aggregation and inhibition of thromboxane B(2) formation was blocked when a single dose of ibuprofen was administered BEFORE aspirin or when multiple doses of ibuprofen were given, but not when the other agents were given or if a single dose of aspirin was given BEFORE the ibuprofen



Catella-Lawson F, et al. Cyclooxygenase inhibitors and the antiplatelet effects on aspirin. NEJM 2001;345(25):1809-1817.

NSAID ADVERSE EFFECTS

- Gastrointestinal complications
 - Risk factors
 - AGE
 - History of PUD
 - Previous NSAID-induced bleeding
 - Concomitant disease (especially cardiovascular)
 - Concomitant steroid use
 - Substantial arthritis-related disability



NSAID ADVERSE EFFECTS

- Salt and water retention
 - Watch in hypertensive patient
 - Watch in patient with CHF
- Renal toxicity
 - Interstitial nephritis
 - Hemodynamic changes
 - Blocks protective role of prostaglandins
- Other
 - Hepatic
 - Platelets
 - CNS
 - Pulmonary



NSAID USAGE RECOMMENDATIONS

- **USE WITH CAUTION**
 - No particular agent lacks potential for serious toxicity.
- Use acetaminophen as first-line agent.
- Consider Cox-2 inhibitors in high risk GI patients,
- caution in high risk CV patients (ibuprofen may cause myocardial scar thinning, infarct expansion and block the antiplatelet effect of ASA)
- Avoid high-dose, long-term NSAIDs use when possible.
 - AGS suggests using selective NSAIDs if long term use needed in older persons
- Use with extreme caution in hypertension, CHF, and hepatic impairment.
- The use of more than one NSAID at a time should be avoided.

TRAMADOL

- Centrally acting synthetic analgesic
- Indicated for moderate to moderately severe pain.
 - Compared favorably with acetaminophen combined with codeine.
- Mechanism of action
 - Opiate receptors
 - Inhibit reuptake of norepinephrine and serotonin



TRAMADOL

- Adverse effects
 - Similar to opioids
 - Less dependency?
 - Increased seizure risk
 - MAOIs and drugs that decrease seizure threshold (tricyclic antidepressants)
 - History of seizures
 - Should not be used with opioids
 - Advantage over opiates?
 - May be useful in neuropathy
- Harati, Y et al. Neurology 1998;50:1842-1846



TRAMADOL

- Dosing (ref # 33)
 - Start slow to prevent light-headedness.
 - 25-50 mg qd - Onset of analgesia may be up to one hour.
 - Stop at effective dose.
 - May not need to go over 200 mg qd (TID dose).
 - Maximum dose in patients >75 yo 300 mg a day.
 - Maximum dose in patients <75 yo 400 mg a day.
 - Seizures occur when dose exceeds recommended doses or if given more than every 4-6 hours.
 - Decrease dose in cirrhosis and renal impairment.
 - **Available as combination with acetaminophen 37.5/325**



OPIOID ANALGESICS

- Pharmacologic activity depends on affinity for opiate receptors.
- Agents do not eliminate pain, but decrease its unpleasantness.
- Agonists have no ceiling dose when it comes to pain relief (exception may be morphine at very high doses)
- Some variability in onset and duration of action.
- **Key to effective use is individualization and proper titration.**

OPIOID ANALGESIC ADVERSE EFFECTS

- Mood changes (minimized with careful titration)
 - Dysphoria (may be seen as agitation in elderly)
 - Euphoria or paradoxical excitement
- Cognitive disturbances (minimized with careful titration)
- Somnolence (minimized with careful titration)
 - Drowsiness
 - Inability to concentrate; apathy
 - Increase in falls

OPIOID ANALGESIC ADVERSE EFFECTS

- Respiratory depression (minimized with careful titration)
- Nausea and vomiting (tolerance usually develops)
- Increased sphincter tone
- Urinary retention
- Histamine release
- Pruritus
 - Rarely, exacerbation of asthma

OPIOID ANALGESIC ADVERSE EFFECTS

- Decreased gastrointestinal motility and secretion
 - Unlike most other adverse effects that are transient or are avoided with careful titration, this IS TO BE EXPECTED!
 - Use an aggressive bowel regimen
 - Lots of fluid
 - Plenty of dietary fiber
 - Stimulants
 - Stool softeners
 - by themselves are often ineffective
 - Bulk-producing laxative ??



OPIOID ANALGESIC ADVERSE EFFECTS

Consensus statement American Academy of Pain Medicine (AAPM), American Pain Society (APS), American Society of Addiction Medicine (ASAM) Feb 2001

- Tolerance – *a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.*
 - Always a possibility
 - Easily confused with change in pain status
 - May be minimized with regular dosing
 - Increase dose to achieve effective analgesia and DO NOT be overly concerned with the size of dose

OPIOID ANALGESIC ADVERSE EFFECTS

Consensus statement American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine Feb 2001

- Physical Dependence – *a state of adaptation that is manifest by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.*
 - Rarely seen with short-term use
 - Slow wean will prevent withdrawal symptoms
 - determined by length of time on therapy and why on therapy

OPIOID ANALGESIC ADVERSE EFFECTS

Consensus statement American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine Feb 2001

- Addiction – *a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.*
 - Inability to take meds as Rx'd, frequent lost/stolen Rx, Doc shopping, isolation, intoxication
 - No single event is diagnostic of addictive disorder, diagnosis is pattern of behavior over time

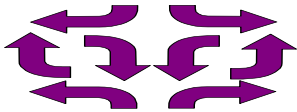
OPIOID ANALGESIC ADVERSE EFFECTS

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 - Usually not seen in chronic pain, risk is unknown, exposure to drugs only one of etiologic factors
 - An individual's behavior that may suggest addiction sometimes a reflection of unrelieved pain or problems unrelated to addiction (**Pseudoaddiction**)

OPIOID ANALGESICS

- Equianalgesic dosing
 - Can use reference guides (better tables being developed)
 - Use only as a guide
 - Individual titration and constant reassessment a must
 - What-How well-How long-End Point



OPIOID ANALGESICS

- Allergies
 - True allergies rare
 - Chance of cross sensitivity decreased between
 - Morphine-like agonists
 - Meperidine-like agonists
 - Methadone-like agonists



MORPHINE

- NOT drug of last resort
- Drug of choice for severe acute pain
- Morphine myths
 - Causes unmanageable side effects
 - It sedates patient too much
 - Morphine causes “addiction”
 - Tolerance a huge problem

MORPHINE

- Metabolism
 - Very little excreted unchanged
 - Morphine-6-glucuronide is renally eliminated
 - decrease dose and careful titrate in patients with renal impairment
- Cardiovascular effects



MORPHINE

- Dosage forms/routes
 - Oral
 - Immediate release
 - liquid/tablet
 - Sustained release
 - q24 vs q12 vs q8
 - Inhalation
 - Rectal
 - Parenteral
 - Subcutaneous/IM/IV, DepoMorphine
 - Epidural/intrathecal



FENTANYL

- Transdermal patch available
 - q 72 hours
 - 12-24 hours to steady state (depots in skin)
 - 6 days after increasing dose to steady state
 - **Chronic nonmalignant pain and cancer pain only**
 - Increased body temperature can change the way patch delivers fentanyl



FENTANYL

- New Formulation (FDA approved November 1998) Oral Transmucosal Fentanyl Citrate (Actiq)-flavored sugar lozenge for treatment of breakthrough cancer pain
 - **Lower strength patch (may be better suited for nursing facility patients)**
 - **Patient-controlled/electrically assisted release mechanism (Iontophoretic transdermal system-available ?)**
 - **Buccal tablets available (not mcg to mcg same as lozenge)**
 - **Some Patches can burn patient in MRI**

CODEINE

- Moderate pain only
 - analgesia due to morphine metabolite
 - antitussive actions probably involve codeine
- Works best when combined with acetaminophen or NSAID
- Watch acetaminophen in combination product
- Same propensity as morphine to produce tolerance, dependence, and constipation

OXYCODONE AND HYDROCODONE

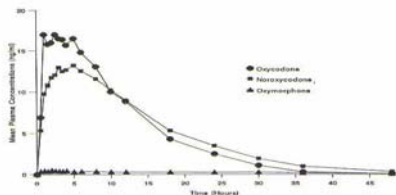
- Most often seen in combination products with aspirin or acetaminophen
- Use in moderate to severe pain
- Different schedules, same efficacy
- Same pharmacology as morphine

SUSTAINED-RELEASE OXYCODONE

- 10, 20, 40, 80 mg dosage forms
 - Q 12 hour dosing
- Breakthrough medication
 - Immediate-release oxycodone
- Use in chronic pain



Kaiko #38



HYDROMORPHONE

- More potent than morphine
- Fast oral absorption
 - Favorite street drug
- Very soluble
 - Use when need a highly concentrated narcotic solution (intrathecal, subcutaneous)
- Pharmacology very similar to morphine
- **Sustained release NOT available (Palladone) Withdrawn from market in 2005**

OTHER MORPHINE-LIKE AGONISTS

- Oxymorphone
 - Can be administered rectally and by injection
 - Offers no advantages over morphine
 - **Extended Release and immediate release oral solids available 2006**
- Levorphanol
 - Extended half-life
 - Effects similar to morphine
 - Should not be used in the elderly as it may accumulate

MEPERIDINE

- Particularly **HAZARDOUS** in the elderly
 - Normeperidine accumulation can lead to delirium and seizures
 - Contraindicated in renal failure
 - Interaction with MAOIs
- Less potent and shorter duration than morphine
 - If administered, should be at higher doses and more often is not
 - Oral dose usually underdosed
- **NO** advantages over morphine



METHADONE

Ref 55,56,57

- Longer duration of action than morphine over time with oral dosing
 - Because of high volume of distribution, get accumulation in tissue
 - Must individually dose because of long unpredictable half-life
- QTc interval prolongation
 - Disclose to all patients
 - Look for history of heart disease, arrhythmias, syncope
 - Pretreatment ECG, follow up 30 days (all patients)
 - Additional ECG follow up > 100 mg day
 - QTc 450 ms – 500 ms consider risks vs benefit
- Increased deaths in northern Michigan
- Can be taken orally or by injection
- Inexpensive
 - 100 tablets AWP 40mg OxyContin=\$440.82
 - 100 tablets AWP 10mg methadone=\$13.74

METHADONE IN OPIOID ROTATION

Ref 55,56

- Dose ratios to achieve equianalgesia influenced by previous opioid
 - Tolerance to opioids may be dependent on NMDA receptor
 - At high morphine doses, metabolites may produce constant activation of NMDA receptor, requiring more MS to maintain pain relief
 - Can even see severe myoclonic jerking
 - Conversion to Methadone (which has NMDA antagonist activity) and no excitatory metabolites can result in dramatic decrease in the MS requirements as excitatory metabolite effects are blunted and over time decreased
 - Has been noted to stop myoclonic jerking
 - Conversion have been made with 3-68% of expected equianalgesic dose

PROPOXYPHENE

- Controversial in nursing facilities **???**
 - Overprescribed in the elderly ??
 - NOT recommended for use in elderly
 - norpropoxyphene can accumulate and cause cardiac toxicity
- **FDA advisory panel recommends banning (2009)**
- For mild-moderate pain
- Same adverse effect profile as other narcotics
- Watch for overdose of acetaminophen/ aspirin in combination product

Medical Marijuana

- New Michigan law (one of 13 states)
- Department of Community Health adopted rules begin April 1
 - Michigan Medical Marijuana Act website
 - Users need state issued certification/ID card
 - Certification must be accompanied with a physician's letter testifying as to why the applicant needs
- Federal law classifies as Schedule 1
- DOES IT HELP With PAIN???

MIXED NARCOTIC AGONIST-ANTAGONISTS

- For moderate to severe pain
- Designed to minimize adverse effects and maximize analgesia
- Ceiling respiratory depression and analgesic effects and may precipitate withdrawal when used with agonists
- Pentazocine **SHOULD BE AVOIDED**
 - Causes delirium and agitation in the elderly
- Butorphanol available intranasally
- In general, these agents should be avoided in nursing facility patients

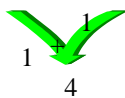
NALOXONE



- Pure narcotic antagonist
- Used to reverse respiratory and sedative effects of opioid analgesics
- Dose must be slowly administered so as not to reverse analgesia
 - 0.4 mg with 10 ml of saline and titrate

COMBINATION THERAPY

- Opioids and non-opioid agents **1**
 - Work better together than alone
 - Combine differing mechanisms of action
 - Acetaminophen, aspirin, ibuprofen
 - Do not be limited by combination products
 - Schedule both opioid and non-opioid
- Opioids and caffeine **4**
 - Additive analgesic effects questionable
- Opioids and stimulants
 - Methylphenidate (5-10mg BID)



ORAL ROUTE OF ADMINISTRATION IS MOST OFTEN THE PREFERRED ROUTE

(in **SOME** chronic pain syndromes, transdermal may be preferred)



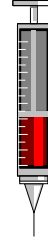
PARENTERAL THERAPIES

- Narcotic infused
 - Morphine vs. fentanyl
 - Solution compounding
- Epidural and intrathecal routes
 - Local anesthetics
 - Clonidine



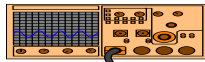
PARENTERAL THERAPIES

- Epidural and intrathecal routes
 - Adverse effects
 - Pruritus
 - Nausea and vomiting
 - Urinary retention
 - Sedation
 - Respiratory depression
 - Other
 - Infection



PARENTERAL THERAPIES

- Epidural and intrathecal routes
 - Patient monitoring
 - Protocols
 - Implantable vs. external pumps



PAIN GUIDELINES

- Acute pain
- Pain in critical care (ASHP)
- Cancer pain
- Arthritis pain
- Neuropathic pain
 - Diabetic neuropathy
 - Post herpetic neuropathy
 - Post stroke/central pain
 - Phantom pain
 - Trigeminal neuralgia
- Low back pain
- Fibromyalgia
- Complex regional pain syndrome



ACUTE PAIN

- Identify the source
- Use the analgesic ladder approach
- Properly titrate and administer for an adequate duration
- Initially, do not use analgesics on an as-needed basis
- Recognize side effects of medications and avoid excessive sedation
- Adjust the route of administration to meet needs of patient
- Assess and reassess!!



CHRONIC/PERSISTENT NONMALIGNANT PAIN

- Chronic pain
 - Many disciplines
 - Frequent use of non-pharmacologic approaches
 - Analgesics + adjuvants



THE PHARMACOLOGIC TREATMENT OF CHRONIC/PERSISTENT PAIN

- Acetaminophen
- NSAIDs/Non-acetylated salicylates
- If non-surgical neurologic involvement
 - Tricyclic antidepressants
 - Anticonvulsants (gabapentin)
- If depression
 - Serotonin transport inhibitors
- Opioids?

TREATING NONMALIGNANT PAIN WITH OPIOIDS

- AAPM AND APS believe Rx of opioids should be extension of good professional practice
 - Evaluation of patient-physical exam, pain history, pain impact on patient, review of previous diagnostic studies, drug history, coexisting diseases/conditions
 - Treatment plan-consideration of all aspects of treatment (behavioral, physical therapy, noninvasive techniques, physical and psychosocial support, and medication)
 - If opioid trial selected risks should be explained to patient and family
 - NO TRIAL WITHOUT COMPLETE ASSESSMENT OF PAIN COMPLAINT

TREATING NONMALIGNANT PAIN WITH OPIOIDS

- AAPM AND APS believe Rx of opioids should be extension of good professional practice
 - Consultation as needed
 - Pain specialist, psychologist, pharmacist
 - Periodic review of treatment efficacy
 - Assess functional state of patient, continued analgesia, side effects, quality of life, indications of medication misuse
 - Documentation
 - Reason for opioid, overall treatment plan, periodic review

BALANCING NEWS STORIES ABOUT OPIOIDS

- Appeal of OxyContin (ref 51)
 - Strength
 - Potential for rapid release
 - High absorption when chewed or snorted
 - Some abusers crush, dissolve, inject
 - 40mg \$25-\$45



BALANCING NEWS STORIES ABOUT OPIOIDS

- FDA, CDC scrutiny (increase in accidental opioid overdoses) (ref 58)
- In US 16,000 die from drug overdoses yearly (ref 52)
 - Usually multiple drug involved
 - Reports in press at times seem exaggerated
- Watch for diversion (ref 54)
 - Patients continually trying to fill Rx early despite dose agreements
 - Frequent reports of lost or stolen Rx
 - Use multiple pharmacies and multiple prescribers
 - Is noncompliant with other treatments
 - Unusual quantity
 - Quantity looks altered
 - Reports allergies to all other drugs



BALANCING NEWS STORIES ABOUT OPIOIDS

- “Taking legal, FDA approved opioid medications as prescribed, under the direction of a physician for pain relief, is safe and effective, and only rarely leads to addiction. When properly used, these medications rarely give a “high”-they give relief. And, most importantly, they allow many people to resume their normal lives”

Dr. James Campell, Professor of Neurosurgery at Johns Hopkins Medical Center, past president Of the American Pain Society, and Chairman of The American Pain Foundation (ref 53)



BALANCING NEWS STORIES ABOUT OPIOIDS

We must be careful not turn the “War on Drugs” into a war on Patients (ref 53)



REASONS FOR OPIOPHOBIA

- Misunderstanding of addiction/dependence
- Misunderstanding of analgesic tolerance
- Misconception that chronic opioid therapy leads to uncontrollable depression, personality changes, and significant impairment of physical and cognitive function
- Lack of information on the correct use of opioids
- Fear of regulatory scrutiny
- Confusion about legitimate prescribing
- Fear of Robbery

NEUROPATHIC PAIN

- Chronic pain secondary to nerve damage
 - Nerve tries to maintain some sensory function but signal perceived as pain
- Symptoms include paresthesias, burning, pins and needles effect
- Very individualized
- Pain concentrated in area of injury
- Onset of pain may be weeks/months after injury

PERIPHERAL vs. CENTRAL NEUROPATHIC PAIN

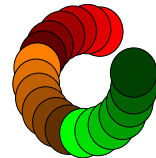
- Peripheral
 - Often referred to as deafferentation pain
 - Examples include: diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia
- Central
 - Post-stroke or spinal cord injury
 - Often occurs in area of sensory loss

TREATMENT

- Medications
 - Topical agents (capsaicin cream, lidocaine)
 - Tricyclic antidepressants
 - Duloxetine
 - Venlafaxine
 - Anticonvulsants
 - gabapentin, pregabalin, carbamazepine, lamotrigine
 - Tramadol
 - Opioids
 - morphine, methadone
 - Antiarrhythmics
 - lidocaine
 - mexiletine
 - Benzodiazepines
 - not recommended

CANCER PAIN MANAGEMENT

- AHCPR guidelines
 - Initiate analgesic ladder
 - Reassessment
 - Palliative therapies as indicated
 - Reassessment
 - Consider other etiologies and treatments
 - Unacceptable side effects
 - Diffuse bone pain
 - Neuropathic pain
 - Movement-related pain
 - Mucositis
 - **REASSESSMENT**



PSYCHOLOGIC AND SUPPORTIVE CARE

- Relaxation training, controlled imagery, biofeedback
 - Work well with pharmacologic agents
- Hospice
 - Family support
 - Acceptance of death and dying
 - Interdisciplinary approach



PRINCIPLES OF PAIN MANAGEMENT

- Always ask patients about pain.
- Always believe the patient.
- Never underestimate potential devastating effects pain may have on a patient's overall condition.
- Be compulsive in assessment.
- An accurate diagnosis will lead to a better treatment outcome.



PRINCIPLES OF PAIN MANAGEMENT

- Use pharmacologic and non-pharmacologic approaches when possible.
- Involve patients in therapy - mobilize them mentally and physically.
- Start drug therapies at low doses and move up slowly.



PRINCIPLES OF PAIN MANAGEMENT

- Use short-acting agents for episodic pain and consider longer-acting agents used around-the-clock for chronic or persistent pain.
- Use caution with NSAIDs.
- Do not be hesitant in considering opioid analgesics for moderate to severe pain.

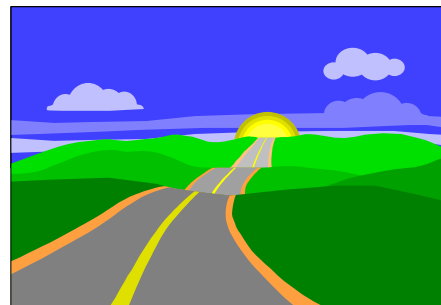


PRINCIPLES OF PAIN MANAGEMENT

- Anticipate drug side effects
 - With opioids--sedation, concentration, constipation.
- Reassess, reassess, reassess.
- Titrate therapy to maximize functional status and quality of life.
- Keep it simple.



SUMMARY



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