Goal

- To provide patients with a level of pain control that allows them to actively participate in recovery
  - This level will be individual to each patient
- To minimize nausea and vomiting
- To minimize other side effects of analgesics
  - Sedation
  - Ileus
  - Weakness
  - Hypotension

OBJECTIVES

- Describe the role of non-opioid pain medications in the care of the “palliative patient”
- Name various categories of non-opioid pain medications
- Identify the indications, safe usage and contraindications of a prototypical medication from each category of non-opioid pain medications
PAIN BASICS

- THREE TYPES OF PAIN
  - Somatic
  - Visceral
  - Neuropathic

- THREE TYPES OF PAIN RECEPTORS
  - Chemical
  - Mechanical
  - Thermal

Pain is a miserable experience
- Pain increases sympathetic output
  - Increases myocardial oxygen demand
  - Increases BP, HR

- Pain limits mobility
  - Increases risk for DVT/PE
  - Increases risk for pneumonia, atelectasis secondary to splinting

- Decreases Quality of Life
- Prevents people from focusing on other difficult decision making

The Nociceptor (J Clin. Invest 2010)

Why all the fuss?

- Pain is a miserable experience
- Pain increases sympathetic output
  - Increases myocardial oxygen demand
  - Increases BP, HR
- Pain limits mobility
  - Increases risk for DVT/PE
  - Increases risk for pneumonia, atelectasis secondary to splinting
- Decreases Quality of Life
- Prevents people from focusing on other difficult decision making
How do we do it?

- **Multimodal analgesia**: Several analgesics with different mechanisms of action, each working at different sites in the nervous system
  - Acetaminophen
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Opioids
  - Anticonvulsants
  - Antidepressants
  - Local anesthetics
  - NMDA Antagonists
  - Non-pharmacologic methods
  - Topical analgesics

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**Multidisciplinary Treatment of Chronic and/or Palliative Pain**

- Pharmacotherapy and other medical/surgical care with appropriate medicine reorganization
- Restorative care including active physical and occupational therapy
- Psychological counseling utilizing cognitive-behavioral pain management strategies

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**OPIOIDS**

Efficacy is limited by Side-Effects

- The harder we “push” with single mode analgesia, the greater the degree of side-effects

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[Diagram showing balance between analgesia and side-effects]
**Multimodal Analgesia**

- Lower doses of each drug can be used therefore minimizing side effects
- With the **multimodal analgesic approach** there is additive or even synergistic analgesia, while the side-effects profiles are different and of small degree (Pasero & Stannard, 2012).

**Pharmacotherapy Guidelines**

1. Medication must result in:
   - Significant pain relief
   - Tolerable side effects

2. Both physician & patient must realize significant individual variability

3. Slow titration until either:
   - Significant pain relief
   - Intolerable side effects
   - “Toxic serum level”

4. Educate the patient, family, caregiver yourselves!
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.

What is “non opioid” pain medication?
- Primary analgesics: NSAIDS, acetaminophen and ASA
- Neuropathic Agents
- Anesthetics
- Antidepressants: TCAs and SNRIs
- Muscle relaxants: Anti-spasticity and anti-spasmodic drugs
- Topicals: lidocaine, NSAIDs, NTG, and aspirin, capsaicin

Non Opioid Medications
- Non opioid pain medications include those medications that are considered by their pharmacologic action to be “analgesics”: Aspirin/non-steroidal anti-inflammatories/acetaminophen
- Adjuvant medications include any category of medication whose primary pharmacologic effect is not analgesia, but has secondary effects that ameliorate pain
What’s in our tool box?

- Non-steroidal anti-inflammatory drugs (NSAIDs and Cox II inhibitors)
- Aspirin (ASA)
- Acetaminophen (APAP)
- Antidepressants
- Neuropathic Agents (Anticonvulsants)
- Muscle Relaxants
- Tramadol
- Topical analgesics

ASA, APAP, “NSAIDs”

- “Prototypical Drugs”: Ibuprofen, Celecoxib, Aspirin, Acetaminophen
- Act by the inhibition of COX-1/2/3 enzymes which convert arachidonic acid to prostaglandins
- Indications and efficacy:
  - Nociceptive pain
  - NNT 2–4 patients for 50% reduction in moderately severe pain
  - All NSAIDs are likely equal in analgesic efficacy

NSAIDS

- Work at site of tissue injury to prevent the formation of the nociceptive mediators Prostaglandins
- Can decrease opioid use ~30% therefore decreasing opioid–related side effects
- Minor surgeries can use NSAIDs instead of opioids to completely eliminate opioid–associated side effects

Coment 2014
cyclooxygenase-2 (COX-2) NSAIDs selectively (primarily) inhibit cyclooxygenase-2 (COX-2) with minimal effect on COX-1 which is responsible for GI and platelet side effects

- Celecoxib

**Adverse effects:**
- GI: ulcerations of gut, hepatitis (fulminant: APAP)
- Renal: renal insuff and interstitial nephritis
- Cardiac: increased risk of MI
  - CoX-2 > non-selective

**Contraindications**
- Gut ulceration
- Bleeding tendency
- Renal disease
- Caution with pregnancy
- Sulfa-Allergy (celecoxib)

**“Pearls”**
- Check CBC, LFTs Chem & periodically
- Consider concommitant PPI/HR blocker
- Beware of elderly patient and consider occult GI bleed with fatigue, weakness or stool changes
- Limit APAP to < 3 gm/d and remember that acetaminophen is “everywhere”

**Anticonvulsants**
- Carbamazepine*
- Divalproex sodium*
- Gabapentin*
- Pregabalin*
- Lamotrigine
- Topiramate*
- Oxcarbazepine
- Topiramate*
- Oxcarbazepine

*Has FDA indication for pain/headache
Clinical Syndromes and Anticonvulsant Use

- Postherpetic neuralgia
  - gabapentin
  - pregabalin
- Diabetic neuropathy
  - carbamazepine
  - phenytoin
  - gabapentin
  - Lamotrigine
  - pregabalin
- HIV-associated neuropathy
  - lamotrigine
- Trigeminal neuralgia
  - carbamazepine
  - lamotrigine
  - oxcarbazepine
- Fibromyalgia
  - pregabalin
- Central poststroke pain
  - lamotrigine

ANTICONVULSANTS (cont.)

- Act by a reduction of neuronal irritability due to flux (Ca++ and Na++) resulting in “membrane stabilizing effect”

Neuropathic Agents: Indications

- Gabapentin/ Pregabalin:
  - PHN, DPN, fibromyalgia
- Valproic Acid, Topiramate:
  - Migraine
- Carbamazepine:
  - Trigeminal neuralgia

Neuropathic Agents

- Gabapentin
  - Binds to a2–d subunit of presynaptic voltage dependent Ca++ channels
  - Reduces the release of glutamate, NE, substance P, dopamine and serotonin
  - Has nothing to do with GABA
  - Uses include:
    - Fibromyalgia (off label)
    - DPN (off label)
    - PHP (FDA)
Neuropathic agents

Gabapentin
- Dosing: start low, go slow
  - Work toward dose of 1800–3600 mg
  - Start doses at night time
  - Adjust for renal creatinine clearance
  - Never stop abruptly
- Adverse Effects
  - Somnolence
  - Can cause: Leukopenia, thrombocytopenia
  - BLACK BOX: increased suicidal thinking
- CONTRAINDICATION
  - RENAL FAILURE

Pregabalin
- Approved indications:
  - PHN, DPN, Fibromyalgia, spinal neuropathic pain
  - Better absorption, decreased somnolence
  - Improved stage IV sleep
- Dosing:
  - 150mg/d in divided doses up to 600mg/d (dx dep)
  - Reduce by 50% if CrCl 30–60 ml/min
- Adverse effects:
  - Somnolence, dysphoria, euphoria
  - Increased risk of angioedema
  - BLACK BOX: increased risk of Suicidal thinking
  - Never Stop Abruptly

Topiramate
- Uses:
  - Migraine prophylaxis (approved)
  - Cluster HA, DPN, neuropathic pain (not approved)
- Dosing:
  - 25–100mg Daily
- Adverse Effects:
  - Acidosis, nephrolithiasis
  - Diminished cognition
  - Reduce dose with renal insuff
  - BLACK BOX: increased suicidal thinking

Carbamazepine/Oxcarbazepine*
- Trigeminal Neuralgia (approved)
- Neuropathic pain (non-approved)
  * Patients of Asian descent should be screened for the variant of HLA–B 1502 prior to therapy

Valproic Acid
- Migraine Prophylaxis (approved)
- DPH/neuropathic pain syndromes (non-approved)

*both drugs are associated with risk of fluid/electrolyte abnormalities, increased suicidal thinking and cbc abnormalities
Antidepressants

- Tricyclics (TCAs – amitriptyline), venlafaxine and duloxetine (SNRIs)
- Thought to cause enhancement of endogenous descending anti-nociceptive systems via inhibition of reuptake of norepinephrine and serotonin

Antidepressant TCAs

- Indication and Efficacy
  - Neuropathic pain*
    - peripheral > central
    - DPN, PHN
  - Other Chronic Pain*
    - Fibromyalgia, LBP
    - HA syndromes
  - NNT (TCA) = 2–4 for 50% reduction in pain
  - Non FDA approved

TCAs cont.

- Consider comorbid conditions when choosing TCA
- doxepin and amitriptyline most sedating and anticholinergic
- Imipramine, nortriptyline and despiramine less sedation and anticholinergic side effects

TCAs cont.

- Dose:
  - Start low and go slow: 10–25 mg
  - For pain lower doses OK (75–100 mg OK)
- Adverse Effects:
  - Sedation
  - Orthostatic hypotension
  - Anticholinergic effects
  - Cardio toxicity
- BLACK BOX WARNING: Increased Suicidal Thinking
TCAs Pearls/ Caution

- Type I Anti-Arrhythmics
- Prolonged PR, QRS, QTc intervals
- Increased risk of cardiac complications when dose > 100mg/d
- Doses below 100mg/d probably safe
- Safe in patients with chronic pain
  (Rev Bras Anestesiol. 2009;46:55)
- EKG in patients >40 years old

SNRI cont.

- Duloxetine
  - Approved for:
    - Diabetic Peripheral Neuropathy treatment
      - 60mg/d resulted in 50% pain reduction
    - NNT: 6
    - Fibromyalgia
      - NNT: 8
    - Chronic Musculoskeletal Pain
  - Dosing: 60mg-90mg/d

SNRI cont.

- Duloxetine adverse effects:
  - Black Box: increased suicidal thinking
  - N/V most common reason for discontinuation
  - Transaminitis
    Do not use in patient with liver disease
  - Adjust dose in patients with severe renal insuff
  - Serotonin Syndrome

SNRIs

- Venlafaxine– Non FDA approved for pain
  - Likely need at least 100mg for pain effect
  - Effective in: DPN, other chronic neuropathy, fibromyalgia, headaches–migraine
  - NNT=3.1
  - Cautions:
    - Can worsen HTN
    - Serotonin Syndrome, especially when taking other serotonin enhancing drugs
    - BLACK BOX: increase suicidal thinking

BLACK BOX: increase suicidal thinking
Currently Available Alpha–Adrenergic Agonists

- Clonidine
- Tizanidine—more commonly used

Possible effective uses of Tizanidine:
- Trigeminal neuralgia (Fromm 1993)
- Chronic low back pain (Berry 1988)
- Cluster headache (D’alessandro 1996)
- Chronic tension–type headache (Nakashima 1994)
- Spasmodic torticollis (Houten 1984)
- Neuropathic pain
- Chronic headache (2002)

- DOSING:
  - 4 mg tid up to 36 mg/d
  - Think clonidine as hypotension very common
  - Titrate dose over 2–4 weeks
  - Watch LFTs and EKG

Muscle Relaxants

- Cyclobenzaprine
- Carisoprodol
- Methocarbamol
- Metaxalone
- Orphenadrine
- Diazepam
- Baclofen

Muscle Relaxants:

- Benzodiazepines
  - Diazepam most commonly used
  - Dosage needed to produce spasmolysis is in excess of 4 mg/d
  - Increased risk of hip fx in elderly
  - Caution if used with opiates!!
- Cyclobenzaprine
  - Think “TCA” Anticholinergic side effects!
  - Efficacious for short term only
- Others
  - Methocarbamol
  - Orphenadrine
  - Metaxalone—mode of action not well understood

Muscle Relaxants:

- Baclofen (GABA–mimetic agent)
  - Inhibits spinal interneuron that stimulates muscle contraction in the reflex arc
  - Multiple sclerosis, other central spastic conditions
- Dosing:
  - Start low, go slow:
    - Maximum dose is 120 mg/d but most clinicians rarely go above 80 mg/d
    - + withdrawal syndrome with intrathecal administration
    - Discontinuation of oral regimen usually results in delayed return of spasticity/ spasms weeks later
Carisoprodol- not recommended

- Precursor of meprobamate (which has been removed from market)
- Centrally active
- Reduction of muscle spasm
- Side effects:
  - Sedation, drowsiness, dependence
  - Withdrawal symptoms
    - Agitation
    - Anorexia
    - N/V
    - Hallucination
    - Seizures

Tramadol (C–VI)

- Centrally acting analgesic
  - Acts as opiate (<< affinity of mu receptor)
  - Primary effect is thought to be via activation of descending inhibitory pain systems like SNRIs
  - Approved for moderate to severe pain
    - generally used with an NSAID in OA
  - Dosage: 50–400mg
  - NNT–6

Tramadol cont.

- Adverse Effects:
  - Somnolence, seizures, N/V, dizziness, constipation,
  - Can be habituating
- Dosage
  - 50–100mg every 4 hrs (max 400mg/d)
- Special considerations
  - Neuro-excitatory properties of Tramadol are increased by SSRIs and to some extent, TCAs
  - Beware of MAOI (linezolid, seligiline)
  - Metabolism by CYP-2D6, CYP-3A4
- Adjustments:
  - Cirrhosis: 50mg q 12hr max 100mg/d
  - Renal Insuff 50–100mg q 12hr max 200mg/d

Topical Analgesics: Key Facts

- Active within the skin, soft tissues and peripheral nerves.
- Does not result in clinically significant serum drug levels.
  - Thus (in general) lack of systemic side effects and drug–drug interactions.
- The mechanism of action of a topical analgesic is unique to the specific agent considered.
Topical Treatments for Chronic Pain

- Diclofenac (patch/gel/lotion)
  - 1.3% patch apply 1 patch to pain site q 12 hrs
  - 1% gel
- Aspirin – over the counter
- Capsaicin
  - 0.025%, 0.075% desensitizes cutaneous nociceptive nerve endings: Must be used daily for several weeks for effectiveness

- Local anesthetics
  - lidocaine patch 5%/eutectic mixture of local anesthetics
- Tricyclic antidepressants – generally available in compounded form only

Summary

- Numerous non opiate pharmacotherapeutic options are available for the management of chronic pain.
- Proper evaluation including pain assessment is key to providing the best analgesic approach.
- Start slow and go slow with most agents
- Optimizing analgesia in the with multimodality therapy is key to achieving a proper balance among efficacy, adverse effects, cost and other factors.

References

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References from Dr Comerci’s portion of slides