Use of Adjuvant and Non-opioid Pain medications in Acute and Chronic Pain

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Objectives

- Describe the physiology of pain perception and how pain progresses from Acute to Chronic.
- Describe the appropriate pharmacological treatment selection of adjuvant and non-opioid pain medications for the management of acute and chronic pain conditions.

Pain: Physiology of Pain Perception
How information travels from tissue damage cells to the CNS

Transduction | Transmission | Perception | Modulation

Basic Processes of Nociceptive Pain - TRANSDUCTION

- Damaged cells release sensitizing substances: Prostaglandins, Bradykinin, Serotonin, Substance P, Histamine
- Neural cell becomes permeable
- Depolarization: Na ion in, K ion out
- Action Potential created
- Conversion of noxious stimuli into electrical action potential

Basic Processes of Nociceptive Pain - TRANSMISSION

- Pain Fiber releases neurotransmitters.
- Glutamate continue the AP across the synaptic cleft to the dorsal horn neurons.
- Ascending fibers continue AP to brain stem to cortex where impulse is processed.
- Pain Fiber Action travels injury site - dorsal horn spinal cord - brain

Transmission Fibers

- **A – Delta Fibers**
  - Fast Transmission
  - Large myelinated fiber
  - Well localized – Initial pain

- **C Fibers**
  - Slow Transmission
  - Small nonmyelinated fiber
  - Lasting, generalized – dull ache

Fibers come into close proximity as they converge on CNS. Cross stimulation can occur: Referred pain, phantom limb pain.
Neuronal Activities in Normal States

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Nerve fiber</th>
<th>Sensation</th>
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<tbody>
<tr>
<td>Low Intensity</td>
<td>A-Beta</td>
<td>Innocuous</td>
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<tr>
<td>High Intensity</td>
<td>A-Delta/C</td>
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Neuronal Activities in Pain States

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<td>A-Beta</td>
<td>Pain (allodynia)</td>
</tr>
<tr>
<td>High Intensity</td>
<td>A-Delta/C</td>
<td>Hyperalgesia</td>
</tr>
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Basic Processes of Nociceptive Pain - PERCEPTION

- Pain perception occurs in the cortical structures
- Huge variety in pain perception
- Brain can accommodate a limited number of signals
- The “feeling” of pain

Gate Theory of Pain
Basic Processes of Nociceptive Pain - MODULATION

Interpretation of the nerve impulse, excitatory or inhibitory

Descending Pathway brain stem to dorsal horn - Inhibition of pain impulse

Release of endogenous opioid, serotonin, and norepinephrine - inhibit substance P

Inhibit the transmission of Nociceptive impulses across the synaptic cleft.

Nociceptive Pain

Somatic Pain
- Stimulation of normal peripheral nociceptors
- Sharp, Aching, Throbbing
- Muscle, bone, Soft tissue
- Easy to localize – can point to pain.
- Non-opioid and/or Opioid responsive.

Visceral Pain
- Stimulation of nociceptors located in the organ systems
- Thorax, abdomen and pelvis
- Dull, aching, throbbing, or cramping
- Pain Radiates
- Non-opioid and/or Opioid responsive.

Neuropathic Pain

Opioid Resistant
- Peripherally Mediated Pain – Diabetic Neuropathy
- Central Mediated Pain – RSD, CRPS, Phantom

Neuronal Processes of Nociceptive Pain

Ongoing negative stimuli

Damage to central nervous system

Burning, numbing, shooting, stabbing, or electrical pain

Endogenous opioids, serotonin, and norepinephrine

Release of endogenous opioid, serotonin, and norepinephrine

Inhibit the transmission of Nociceptive impulses across the synaptic cleft.

Cellular Changes in Chronic Pain

Acute Pain
- Glutamate

Chronic Pain
- Substance P

NMDA, AMPA, Calcium Channels

Nitric Oxide Synthase

c-fos Gene Expression
Chronic Neuropathic Pain: Control Versus Fibromyalgia Patient

Comparably, noxious stimuli

How do you treat this?

Pharmacologic Approach to Pain Management – Where do they work?
Tricyclic Antidepressants

MOA: Modulation:
- Inhibits reuptake of serotonin and norepinephrine
- Inhibits Substance P
- Inhibits transmission of Nociceptive impulses across the synaptic cleft
- Sodium channel blocker

Place in therapy
- 1st line therapy for Neuropathic Pain
- DPN, PHN, Polyneuropathy, Postmastectomy pain, Central post-stroke pain
- Depressed patients/insomnia

Dose
- Effective pain dose lower than depression dose - starting 25 mg/HS up to 100 mg/day
- Start low, go slow, titrate slowly 3-7 days
- Adequate Trial: 6-8 wks – Max. tolerated dose for 2 weeks.

Advantages
- Efficacy
- Low Cost
- Once Daily Dosing
- Beneficial effects on depression, insomnia

Disadvantages
- Precautions: Glaucoma, suicide risk, seizure disorder, concomitant use of Tramadol.
- Amitriptyline: Avoid in elderly
- AE: Sedation, dry mouth, blurred vision, weight gain, urinary retention, orthostatic hypotension
  - NeuPSIG- secondary amine TCAs Nortriptyline and desipramine
- Cardiac Toxicity – NeuPSIG Guidelines
  - Caution in cardiac disease/ventricular conduction abnormalities
  - Limit doses to 100 mg/day
  - EKG for pt>40 years
SSNRI: Selective Serotonin and Norepinephrine Reuptake Inhibitors

**MOA - Modulation**
- Inhibits reuptake of serotonin and norepinephrine
- Inhibits Substance P, inhibits transmission of impulses across the synaptic cleft

**Places in Therapy**
- Duloxetine and Venlafaxine – 1st line NP w or w/o depression
- Milnacipran – Indicated for fibromyalgia

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**Duloxetine**

- Depression, DPN, Fibromyalgia (benefit not seen in men)

**Advantages:**
- Improvement of depression
- Dosing: 30mg/day – inc. to 60 mg/day in 1wk., Max dose: 60mg bid.
- Duration of adequate trial – 4 weeks
- No CV effects

**Disadvantages:**
- Adverse Effects:
  - Nausea
  - Headache, dizziness, insomnia, weight gain long term
- Precautions: Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of Tramadol
- RCTs only in DPN

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**Venlafaxine (Effexor®)**

- DPN, Polyneuropathy

**Advantages:**
- Short and Long acting preparations
- Duration of Adequate Trial - 4 weeks
  - Dose: Initiate 37.5 mg qd-bid, inc. 75mg q week, Max Dose is 225mg/day
- Improvement of depression

**Disadvantages:**
- Not FDA approved for CP
- RCTs not effective-PHN, Post mastectomy pain
- Lower norepinephrine levels esp. in lower doses.
- AEs: Nausea, Cardiac conduction abnormalities, increased bp
- Precautions: Concomitant use of Tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation

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**NeuPSIG Guidelines**

**First Line**
- TCA/SSNRI
- Antidepressants
- Anticonvulsants (Ca channel)
- Topical Lidocaine

**Second Line**
- Tramadol and Opioids

**Third Line**
- Antidepressants
- Anticonvulsants
- Capsaicin
- Mexiletine
- NMDA receptor antagonists
Calcium Channel Alpha 2- Ligands
Gabapentin and Pregabalin

MOA - Transduction
• Binds to Voltage-gated Calcium Channel and Block impulse

Place in Therapy
• 1st line in patients without depression

Organ Involvement
• Dose reduction in renal impairment

Side Effects
• Ataxia, dizziness, sedation and unclear thinking

No Significant Drug Interactions

Sleep Modulating agents

Gabapentin

<table>
<thead>
<tr>
<th>FDA</th>
<th>PHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional RCTs</td>
<td>DPN, Polyneuropathy, Phantom Limb Pain, Guillain-Barre syndrome, Neuropathic Cancer pain, spinal cord injury pain and multimodal acute post op pain. Not effective CRPS I, Chemotherapy induced neuropathy, HIV neuropathy.</td>
</tr>
<tr>
<td>Dosing</td>
<td>Nonlinear Starting dose: 100-300 mg hs, Increase by 100-300mg q1-7 days up to 1200 mg TID</td>
</tr>
<tr>
<td>Trial Duration</td>
<td>3-8 weeks titration plus 2 weeks at max dose</td>
</tr>
<tr>
<td>Scheduled</td>
<td>Not</td>
</tr>
</tbody>
</table>

Pregabalin

<table>
<thead>
<tr>
<th>FDA</th>
<th>DPN, Fibromyalgia, and PHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>Linear Starting Dose: 50 mg tid ; Increase to 100mg TID in 1-7 days Max Dose 600mg/day.</td>
</tr>
<tr>
<td>Trial Duration</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Scheduled</td>
<td>C-V, Euphoria noted; improvement in anxiety</td>
</tr>
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NeuPSIG Guidelines

First Line
- TCA/SSNRI Antidepressants
- Anticonvulsants (Ca channel)
- Topical Lidocaine

Second Line
- Tramadol and Opioids

Third Line
- Antidepressants
- Anticonvulsants
- Capsaicin
- Mexiletine
- NMDA receptor antagonists

5% Lidocaine Patch

MOA Transduction:
• Sodium channel blockade in damaged peripheral nerves
• Mechanical barrier decreases alldynia

Place in Therapy
• FDA approved for PHN, Polyneuropathy
• Not effective for Central NP

Dose
• Apply up to 3 patches daily for up to 12 hours, Patches may be cut
5% Lidocaine Patch

**Advantages**
- Little (3%) systemic absorption
- Titration not necessary;
- Adequate trial: 3 weeks

**Disadvantages**
- Redness or rash at the site of application

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**Second Line – Opioid/Tramadol**

1st Line
- Acute neuropathic pain
- Neuropathic Cancer pain
- Episodic exacerbations
- Pain relief during titration of first line medications

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**Third Line**

- Single RCTs shown efficacy:
  - Antidepressants SSRIs
  - Antiepileptic Na Channel
  - Topical Capsaicin/ High Concentration Capsaicin Patch
  - NMDA antagonist
  - Memantine
  - Mexiletine
  - Botulinum Toxin
  - Lacosamide

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**AD – SSRI: Selective Serotonin Reuptake Inhibitor**

- Modulation: Inhibits reuptake of serotonin
  - Inhibits Substance P
  - Inhibits transmission of nociceptive impulses across the synaptic cleft
- Analgesia not well established
- Medications:
  - Fluoxetine
  - Sertraline
  - Escitalopram
  - Citalopram
Antiepileptic Drugs

- Transduction: Binds to Sodium Channel and Blocks impulse with other mechanisms
  - Carbamazepine: FDA approved for trigeminal neuralgia
  - Toprimate
  - Lamotrigine
  - Zonisamide
  - Oxcarbazepine

Milnacipran

- Approved for fibromyalgia not depression
- SSNRI - NE selectivity - Different MOA than Duloxetine
- Reduced fibromyalgia pain who did not have depression or anxiety.
- 50mg qd – 50 mg BID – up to 100 mg bid.
- Less Side Effects

Anticonvulsants - other

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Evidence</th>
<th>SE</th>
</tr>
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<tbody>
<tr>
<td>Lamotrigine</td>
<td>Na blocker</td>
<td>++HIV NP</td>
<td>Black box warning skin rashes, many SE</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Na blocker, Ca blocker</td>
<td>+</td>
<td>Common SE, significant hyponatremia</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Na glutamate, GABA</td>
<td>+</td>
<td>MANY SE and DI decrease serum bicarbonate</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Na blocker, Ca blocker</td>
<td>+</td>
<td>Sulfonamide reactions – Stevens Johnson Syndrome, common SE</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Na blocker, Ca blocker</td>
<td>+++ TN +NP</td>
<td>Potential fatal blood dyscrasias, potential Stevens Johnson, Many SE</td>
</tr>
</tbody>
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Capsaicin

- Naturally-occurring derived from hot chili peppers
- MOA: Stimulates unmyelinated C fibers in afferent neurons, causes release of Substance P.
  - Repetitive topical application over several weeks to painful intact skin depletes substance P stores. Reduces the transmission of painful stimuli from peripheral nerve to CNS
  - burning sensation until substance P is depleted
Capsaicin Cream and Patch

- Cream: 0.025% -0.075% capsaicin in lidocaine no prescription required
  - Apply thin film 2-4 times daily

- Capsaicin patch 8% Rx: single one hour treatment-sustained reductions in pain that persists 2-3 months –repeat doses causes heat pain sensation loss
  - Approved for post herpetic neuralgia
  - Also used in diabetic neuropathy, osteoarthritis

Nociceptive/Neuropathic Acute Pain

Opioids plus

- NSAIDs
- APAP
- NMDA antagonist
- Lidocaine

NMDA Receptor Antagonists

Transmission: Inhibition of windup caused by activation of NMDA receptors. Blocks glutamate at postsynaptic receptor.

- Use in NP, preemptive postoperative pain, fibromyalgia

- Ketamine, Amantidine, Dextromethorphan,
  - Subanesthetic doses of ketamine reduce morphine in the first 24 hrs after surgery.
  - Oral Ketamine for neuropathic pain 0.25mg/kg tid – use iv solution

- Light headedness, dizziness, tiredness, headache, nervous floating feeling, bad dreams

- Many new agents being investigated.

Overview of Nonopioids

Acetaminophen (APAP) and NSAIDs

- All are effective against nociceptive pain
- No evidence for effectiveness against neuropathic pain
- All have an analgesic ceiling
Multimodal approach should be employed which includes non-opioids and local anesthetics.
Regional blockade should be considered.
Unless contraindicated, all patients should receive ATC NSAIDs, COX-2 inhibitors, or acetaminophen.
Oral NSAIDs, COX-2 inhibitors or Acetaminophen plus oral opioids.
- Optimize efficacy
- Minimize adverse effects.

Effective for mild to moderate postoperative pain
Favorable side effect profile
No drug-drug interactions
No significant effects on platelet aggregation – advantage when surgical bleeding is an issue
NO MEDICATION SHORTAGE

IV Acetaminophen
- Effective for mild to moderate postoperative pain
- Favorable side effect profile
- No drug-drug interactions
- No significant effects on platelet aggregation – advantage when surgical bleeding is an issue
- NO MEDICATION SHORTAGE

Effective for mild to moderate postoperative pain
Favorable side effect profile
No drug-drug interactions
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NO MEDICATION SHORTAGE
Postoperative plasma paracetamol levels following oral or intravenous paracetamol administration: a double-blind randomized controlled trial
Brett et al, Anaesthesia and Intensive Care 2012

- 30 patients undergoing knee arthroscopy
- Two arms either IV APAP 1000 mg intraoperatively or PO APAP 1000 mg 30-60 minutes preoperatively
- Plasma APAP levels were significantly greater in the IV APAP group
- All patients in IV APAP group reached therapeutic levels, while less than half in the PO APAP group reached therapeutic levels
- Trends toward reduced rescue analgesia and recovery room stay in the IV APAP group
- No difference in pain scores in recovery room between groups

Intravenous acetaminophen reduced the use of opioids compared with oral administration after coronary artery bypass grafting.

- 80 pt randomized 2 groups 1 gm every 6 hours either po or IV after extubation.
- IV group received less opioids 17.4 mg vs 22.1mg IV MS equiv. but PONV incidence and VAS scored did not differ.
- Conclusion: IV APAP had a limited opioid sparing effect and was not accompanied by decrease in PONV incidence – clinical significance of the opioid sparing effect is questioned.

Preemptive analgesic effects of IV paracetamol in TAH
Arici et al 2009 – R, DB, P-C parallel study

- 90 pt undergoing TAH randomized APAP 1000mg 30 min prior to induction, APAP 1000mg prior to skin closure or placebo
- Post-operative PCA morphine consumption was significantly higher in intraoperative and placebo group compared to the prior to induction group

Combining paracetamol with NSAIDs: a qualitative systematic review of analgesic efficacy for acute postoperative pain
Anesth Analg: 2010; 110(4) 1170-9

- Primary outcome measures: PID scores and Supplemental analgesic requirements. Studies looked at po/iv, po/po, iv/iv
- Subgroup-14 studies NSAIDs/Paracetamol vs. NSAIDs alone.
- 9 of the 14 studies: combination more effective than NSAIDs alone
  - 2 of the 9 studies had conflicting results
- Subgroup – 20 studies NSAIDs/Paracetamol vs. Paracetamol alone.
- 17 out of 20 studies: combination more effective than Paracetamol alone.
  - 4 of the 17 studies had conflicting results
- Authors concluded evidence suggests combination of paracetamol and an NSAID may offer superior analgesia compared with either drug along
Postoperative analgesia with parecoxib, acetaminophen, and the combination of both: a randomized, double blind, placebo controlled trial in patients undergoing thyroid surgery

Gelding, Br J Anesh 2010: 104;761-7

- 140 patients
- 4 arms
- Placebo, or acetaminophen IV 5 gm/24hr, or parecoxib IV 80mg/24hr or both.
- All three arms were significantly reduced opioid requirement compared to placebo.
- Combination did not have any advantage over individual.

Intravenous acetaminophen vs oral ibuprofen in combination with morphine PCA after Cesarean delivery.

Alhashemi, Can J of Anes 53(12) 2006

- 45 pts 2 arms
  - APAP 1Gm IV q6h plus oral placebo
  - Ibuprofen 400 mg po q6h plus IV placebo
  - 1st dose given 30 min pre op.
- VAS –no significant difference between groups at any time in study period (0-48 hours) P=0.124
- No significant difference between cumulative doses of postoperative Morphine P=0.628
- No significant difference with patient satisfaction between the two groups P=0.93

The Effects of Oral Ibuprofen and Celecoxib in Preventing Pain, Improving Recovery Outcomes and Patient Satisfaction After Ambulatory Surgery

White P Anesth Analg 2011

- 180 pts 3 arms – control, celecoxib 400mg in RR + celecoxib 200 mg bid, ibuprofen 400mg in RR + 400mg TID. X3days
- Both active groups significantly decreased need for analgesic rescue leading to an improvement in quality of recovery and patient satisfaction

What non-opioid should be used for multimodal acute pain?

- IV Ketorolac
- COX-2 po
- NSAID po
- Ibuprofen IV
- Acetaminophen IV
- Acetaminophen po
Questions?