Gastroenterology Pain Points

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Disclosures

**Speaker** for Insys, Iroko, Takeda

**Consultant** for Insys, Quest Diagnostics
Structure of this talk

- NSAIDs, COX 2, Acetaminophen in GI
- Opioids in GI
- Cyp P-450 and opioids
- Fentanyl and buprenorphine
- Limbic system and pain
- Central sensitization

- Topical medications
- Anticonvulsants
- Antidepressants
- Dopamine blockers
- Antianxiety
- Stimulants
- Antiaddiction meds
Goals of Pain Management

- Decrease pain
- Increase function
- Utilize medications that limit unacceptable side effects, including addiction
NSAIDs associated mortality

- Literature reports 16,500 deaths annually as a result of NSAID-induced GI bleeding
  Data from the Arthritis, Rheumatism, and Aging Medical Information System, 1999

- An alternative estimate reports a smaller number of 3,200 deaths annually

- An overall mortality incidence rate of 48/1,000 person-years was reported for patients taking non-selective NSAIDs compared with 75/1,000 person-years with opioids
Acetaminophen

- **Use**
  - For mild-to-moderate pain
  - Efficacy comparable to NSAIDs in some musculoskeletal conditions
  - Common combination drug (eg, hydrocodone)

- **Safety**
  - Few adverse effects
  - Hepatic toxicity possible at high doses (> 4 g/d) or with chronic alcohol abuse
  - Acetaminophen can interrupt the fundamental capacity to empathically connect with other people's painful experiences

- **Dosage**
  - Up to 4 g/d in divided doses in acute use;
  - Up to 3 g/d in divided doses in chronic use;
  - Lower dose in elderly, dehydration or liver disease

**Acetaminophen**

Mechanism of action

- A centrally acting analgesic, increasing the pain threshold

- Mechanism of action is not known but may involve nitric oxide, NMDA, substance P, and antagonism of COX-2 and COX-3 enzymes

COX-2 Inhibitors

- Lack of inhibition of platelet aggregation
  - Protection from longer bleeding times

- Lack of effect on gastric mucosa
  - Protection from ulcers and GI bleeds
  - However, combination with even low dose aspirin (ASA) reduces this protection
Levels of COX-1 Inhibition

Levels of COX-2 Inhibition\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Medication</th>
<th>Inhibition %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam 15 mg QD</td>
<td>78%</td>
</tr>
<tr>
<td>Diclofenac 50 mg TID</td>
<td>94%</td>
</tr>
<tr>
<td>Ibuprofen 800 mg TID</td>
<td>71%</td>
</tr>
<tr>
<td>Naproxen 600 mg BID</td>
<td>72%</td>
</tr>
<tr>
<td>Celecoxib 200 mg BID</td>
<td>74%</td>
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Degree of COX Selectivity Among Common NSAIDs

Y-Axis = Log (IC$_{80}$ Ratio, Human Modified Whole Bloody Assay COX-2/COX-1)

Adverse Events with NSAIDS


**Gastrointestinal**

<table>
<thead>
<tr>
<th>Days of NSAID Use</th>
<th>Adjusted OR for bleed, perf, or ulcer</th>
</tr>
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<tbody>
<tr>
<td>1-14</td>
<td>3.1</td>
</tr>
<tr>
<td>15-30</td>
<td>2.9</td>
</tr>
<tr>
<td>31-60</td>
<td>2.1</td>
</tr>
<tr>
<td>61-90</td>
<td>2.5</td>
</tr>
<tr>
<td>91-120</td>
<td>2.25</td>
</tr>
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</table>

**Cardiovascular**

<table>
<thead>
<tr>
<th>Days of NSAID Use</th>
<th>Adjusted OR for MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-14</td>
<td>1.39</td>
</tr>
<tr>
<td>15-30</td>
<td>1.2</td>
</tr>
<tr>
<td>31-90</td>
<td>1.25</td>
</tr>
<tr>
<td>91-180</td>
<td>1.54</td>
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**Renal**

<table>
<thead>
<tr>
<th>Days of NSAID Use</th>
<th>RR for Acute Renal Failure</th>
</tr>
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<tbody>
<tr>
<td>1-30</td>
<td>2.65</td>
</tr>
<tr>
<td>31-365</td>
<td>2.42</td>
</tr>
<tr>
<td>366-730</td>
<td>4.33</td>
</tr>
<tr>
<td>&gt;730</td>
<td>3.71</td>
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</tbody>
</table>

GI Risk of Individual NSAIDs by Dose

In a recent systematic review of observational studies, the risk of NSAID-induced GI events (perforations, ulcers, bleeds) was generally shown to be dose related.

Graph adapted from Castellsague J, et al. 2012.

Note: The meta-analysis in Appendix B indicates that the RRs for diclofenac are likely less than in this slide, more in line with celecoxib (Dr. James R. Miller)
NSAIDs Adverse Effects
Dose-Related

• **GI events (Upper GI)**
  Odds ratio (OR), which estimates Relative Risk (RR)
  \[ \times 2.4 \text{ in low/medium dose} \]
  \[ \times 4.5 \text{ in high dose} \]

• **MI events** (Myocardial Infarction is one type of CV event)
  Odds ratio (OR), which estimates Relative Risk (RR)
  \[ \times 1.2 \text{ in low dose} \]
  \[ \times 1.6 \text{ in high dose} \]
NSAIDs Adverse Effects

**GI**

- 60-80% of Gastrointestinal bleeds are silent
## Historical Approaches to Mitigate NSAID Risk

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Benefits</th>
<th>Risks</th>
</tr>
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<tbody>
<tr>
<td>Enteric Coating</td>
<td>Potentially reduce upper GI events but do not protect against lower GI, CV, or renal events</td>
<td></td>
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<tr>
<td>Pro-Drug (ex: nabumetone)</td>
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<tr>
<td>NSAIDs + Gastro-protective Agents</td>
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<tr>
<td>COX-2 Inhibitors</td>
<td>May reduce GI events but potential to increase CV &amp; renal risks</td>
<td></td>
<td></td>
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<tr>
<td>Topical NSAIDs</td>
<td>Localized delivery but may have limited utility depending on location of pain</td>
<td></td>
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</tbody>
</table>

### Lowering The Dose While Offering Efficacy Offers a Promising Approach

References:
4. RTI Cost Effectiveness Report. Iroko Pharmaceuticals, LLC.
Mitigating Risk
NSAIDS with Shorter T-1/2 are Safer

A shorter half-life is *generally* associated with a decreased risk of GI adverse effects

**Short T-1/2**
- **2h** Diclofenac (Voltaren)
- **2-6h** Ketorolac (Toradol)
- **3-4h** Ibuprofen (Advil, Motrin)

**Long T-1/2**
- **12-17h** Naproxen (Aleve, Naprosyn, etc.)
- **15-20h** Meloxicam (Mobic)
- **50h** Piroxicam (Feldene)

Note: In addition to half-life, the risk associated with a particular NSAID can be influenced by its dosage, its duration of use, and its relative selectivity for the COX-1 versus COX-2 enzymes.
Mitigating Risk
Be cautious combining medications

- Combo of NSAIDs and ASA significantly increases GI risks (Need 2h break in between doses of NSAID and ASA)

- Avoid drug interactions by knowing potential interactions and taking a good history of medications
OPIATE RECEPTOR

- Increase in tolerance
- Agitation
- Hallucinations
- Irritability
- Insomnia
- Edema
- Muscle twitching
- Sweating
- Rash
- Nausea
- HA
- Itching
- GI spasm
- Urinary retention

Pain control
- Sedation
- Mental slowing
- Fatigue
- Weight gain
- Constipation
- Weakness
- Miosis
- Dry skin
- Dry mouth
- Respiratory depr
- Hypotension
- Cough suppression
- Testosterone suppr.
GI Adverse Effects Mechanism

- Increase in smooth muscle tone in the antrum of the stomach and duodenum
- Inhibition of propulsion
- Increase in colon tone up to a spasm
- Reduction of gastric, biliary, pancreatic secretions
- Spasm of the sphincter of Oddi
- Increase in GI related pain due to above
GI Adverse Effects

**Inhibitory**
- Constipation
- Bloating
- Dry mouth
- Teeth decay

**Excitatory**
- Nausea, vomiting
- Hiccups
- Laxatives
- Senokot –S (colace+senna)
- Reglan 5-10mg po Q6-8h prn
- Bentyl 10-20mg po QID
- E-mycin, Biaxin
- Naltrexone regular doses
- Methylnaltrexone
- Phenergan 25 mg po Q4-6h prn, Compazine 5-10mg po Q6-8h prn,
- Zofran 8-24 mg po Q8h
- 1st generation antipsychotics
- Naltrexone nano doses
Hiccups (singultus or opioid induced myoclonus of diaphragm)

- Opioid and opioid neuroexcitatory metabolites agonise mu2 receptors in the medulla, which activates inspiratory muscles (diaphragm and intercostal) which makes hiccups begin (1)
- Opioids change the post-synaptic pain transmission in dorsal horn neurons via glycine and/or NMDA receptors (act in non-opioid receptors)(2)
- Not clearly opioid related mechanisms: Possible unknown opioid receptor activation; interaction with cancer drugs; abnormal metabolism of opiates (3,4,5)

Most Potent Opioids

- Morphine 1 68% receptor binding
- Alfentanyl 30
- Fentanyl 100 81% receptor binding
- Sufentanyl 1000
- Carfentanyl 8000 98% receptor binding
- R 51703 (“taming drug”) - Janssen
Cyptoheptadine P-450 2D6

Inhibitors
- Paroxetine
- Fluoxetine
- Duloxetine
- Sertraline (high doses)

Substrates
- Hydrocodone (1, 2)
- Oxycodone
- Tramadol (1)
- Codeine (1, 3)

1. Prodrug, has to be metabolized into active compound
2. Also minimally metabolized by 3A4
3. Only 5-10% is metabolized into morphine, the rest is metabolized by glucoronidation
Cyptoheptadine P-450 3A4

Inhibitors

- Fluvoxamine
- Ketoconazole
- Methadone
- E-mycin

Substrates

- Methadone *
- Fentanyl *
- Meperidine
- Buprenorphine

*Also minimally metabolized by 2D6
Fentanyl

- Synthesized by Paul Janssen in 1959
- Creates a tissue depot
- Less GI and skin AEs
- Used: IV, SL, transdermal, buccal, nasal spray, mouth floor spray, inhaler
- Cyp P450 3A4 metabolized
- Careful in poor metabolizers
- Careful with inhibitors, including ketoconazole, fluvoxamine, erythromycin, grapefruit juice, etc.
- Adjust with inducers, including tobacco, carbamazepine, phenobarbital and modafinil

2. Modified from Pain Physician 2011; 14:E343-360
3. Expert Review Neurother. 2011 Aug;11(8);1197-216
5. Pain Physician 2008: Opioid Special Issue: 11:S133-S153
Buprenorphine - Suboxone, etc.

- Unveiled in 1971, on GB market since 1978. In the US liquid form was in use since 1980s and from 2002 – sublingual
- Patch form for pain in Europe since 2001 – 35; 52.5 and 70mcg
- Partial Mu agonist, kappa antagonist
- Administration: IV, SL, transdermal, intrathecal in India
- Metabolized by P-450 3A4
- Possible QT prolongation
- Mood improvement
- Lesser euphoria
- Poorly antagonized by naloxone
- Lesser abuse potential

2. Modified from Pain Physician 2011; 14:E343-360
Buprenorphine

- 30-50 times potency of MS
- Suppresses hyperalgesia
- Up regulates mu receptors (1)
- Facilitates mu receptors migration to cell membranes (2)
- Significantly alleviates more pain types than fentanyl (3)
- Pronounced antihyperalgesic effect because of kappa antagonism (4)
- Not as immunosuppressive as morphine (5)

MOR migration
References


42. Thomas JM, Hoffman BB: Buprenorphine prevents and reverses the expression of chronic endorphine-induced sensitization of adenylyl cyclase in SK-N-SH human neuroblastoma cells. J Pharmacol Exp Ther. 1993;264(1);368-374


Limbic System

Caudate Nucleus

Thalamus

Locus Ceruleus

Regulation:
- Pain
- Sleep
- Stress Response

* Dopamine
** Endorphins
*** Norepinephrine
**** Glutamate/GABA

Interneurons and Glia
Multidisciplinary Treatment of Chronic 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
Topical Lidocaine Patch 5%

- Lidocaine 5% in pliable patch
- Up to 3 patches applied once daily directly over painful site
  - 12 h on, 12 h off (FDA-approved label)
  - published data indicate 4 patches (18–24h) safe
- Systemic side effects unlikely
  - most common side effect: application-site sensitivity
- Clinically insignificant serum lidocaine levels
- Mechanical barrier may decrease allodynia
<table>
<thead>
<tr>
<th>Anticonvulsants</th>
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<tbody>
<tr>
<td>Carbamazepine (Tegretol®)</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal®)</td>
</tr>
<tr>
<td>Gabapentin (Neurontin®)</td>
</tr>
<tr>
<td>Pregabalin (Lyrica®)</td>
</tr>
<tr>
<td>Tiagabine (Gabitril®)</td>
</tr>
<tr>
<td>Topiramate (Topamax®)</td>
</tr>
<tr>
<td>Zonisamide (Zonegran®)</td>
</tr>
<tr>
<td>Levetiracetam (Keppra®)</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal®)</td>
</tr>
<tr>
<td>Valproic acid (Depakene®)</td>
</tr>
<tr>
<td>Divalproex Na (Depakote®)</td>
</tr>
<tr>
<td>Lacosamide (Vimpat®)</td>
</tr>
<tr>
<td>Eslicarbazepine (Aptiom®)</td>
</tr>
<tr>
<td>Ezogabine (Potiga®)</td>
</tr>
<tr>
<td>Perampanel (Fycompa®)</td>
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Anticonvulsants
Central Sensitization on Spinal Level

- Persistent activation of C-fiber sensory nerves
- Sensitizes neurons in the dorsal horn of the spinal cord
- Exaggerated neuronal response to normal input
- Damage to sensory nerves may result in aberrant firing, which can trigger central sensitization and develop into neuropathic pain
- Decrease in Na
- Decrease in Mg
- Increase in NO

Central Sensitization on Brain Level

- Prolonged dopamine elevation
- Prolonged endorphins elevation
- Decrease in GABA
- Prolonged increase in glutamate
- Decrease in NE and 5HT production
- Glia involvement (CCK-7; TNF; etc.)
- Thalamic hyperactivity
- Generalization of response
Enhancement of GABA-Mediated Neurotransmission

- Direct stimulation of the GABA receptor
  - GABA agonist (eg, THIP)
- Modulation of the GABA receptor
  - Increase sensitivity (eg, benzodiazepines)
- Inhibition of GABA metabolism
  - GABA-T inhibition (eg, vigabatrin)
- GABA analog (baclofen)
- Inhibition of GABA reuptake into the presynaptic neuron and glial cells
  - Bind to GAT transporters (eg, tiagabine)
Antidepressants

**TCA**
- Amitriptyline (Elavil®)
- Nortriptyline (Pamelor®)
- Imipramine (Tofranil®)
- Desipramine (Norpramin®)
- Doxepin
- Protriptyline (Vivactil®)
- Clomipramine (Anafranil®)

**Odd balls**
- Mirtazapine (Remeron®)
- Vilazodone (Viibryd®)
- Vortioxetine (Brintellix®)
- Agomelatine (Valdoxan®)
- MAOI’s
- Selegilene (Emsam®)
- Bupropion (Wellbutrin®, Zyban®, Aplenzin®, etc.)

## Dopamine blocking agents

### Atypicals
- Haloperidol (Haldol®)
- Fluphenazine (Prolixin®)
- Chlorpromazine (Thorazine®)
- Droperidol (Inapsine®)
- Promethazine (Phenergan®)
- Prochlorperazine (Compazine®)
- Pimozide (Orap®)
- Loxapine (Loxitane®)
- Quetiapine (Seroquel®)
- Olanzapine (Zyprexa®)
- Clozapine (Clozaril®)
- Ziprazidone (Geodon®)
- Asenapine (Saphris®)
- Risperidone (Risperdal®)
- Paliperidone (Invega®)
- Aripiprazole (Abilify®)
- Lurasidone (Latuda®)

### References
- Desai PM, Desai KP. Combined fluphenazine and lidocaine for pain relief in head and neck cancers. Trop Doct. 2000 Apr;30(2):69-70
- Viisanen H, Ansah OB, Pertovaara A. The role of the dopamine D2 receptor in descending control of pain induced by motor cortex stimulation in the neuropathic rat. Brain Res Bull. 2012 Nov 1;89(3-4):133-43.
Caveat

Anything that can help depression, anxiety, PTSD and psychosis can help chronic pain
Anti-anxiety

- Alprazolam (Xanax®)
- Lorazepam (Ativan®)
- Diazepam (Valium®)
- Clonazepam (Klonopin®)
- Chlordiazepoxide (Librium®)


Hydroxyzine (Vistaril®, Atarax®)
- Buspirone (Buspar®)
- Valerian
- Formula 303®
- Quetiapine (Seroquel®)

Lavin RA, Tao XG, Yuspeh L, Bernacki EJ. Impact of the combined use of benzodiazepines and opioids on workers’ compensation claim cost. J Occup Environ Med. 2014 Sep;56(9):973-8


Nayebi AM, Rezazadeh H, Nourafkan M. Buspirone attenuates tolerance to analgesic effect of morphine in mice with skin cancer. Pak J Pharm Sci. 2010 Apr;23(2):201-6

Stimulants

Scheduled

- Methylphenidate (Ritalin®, Concerta®, etc.)
- Dextroamphetamine (Adderall XR®, Dexedrine®, etc.)
- Lisdexamphetamine (Vyvanse®)

Non-scheduled

- Atomoxetine (Strattera®)
- Modafinil (Provigil®)
- Armodafinil (Nuvigil®)
- CoQ-10
- Ginkgo Biloba


Anti-addictions

- Naltrexone (ReVia®)
- Naltrexone monthly (Vivitrol®)
- Buprenorphine (Subutex®, Suboxone®, Zubsolv®, etc.)