Non-Opioid and Alternative Approaches for Pain
Collaborators

Milken Institute School of Public Health

THE GEORGE WASHINGTON UNIVERSITY

GEORGETOWN UNIVERSITY
More resources available at the DC Center for Rational Prescribing

doh.dc.gov/dcrx
Course Faculty

• Raymond Dionne, DDS, MS, PhD
• Adriane Fugh-Berman, MD
• Susan Wood, PhD
Important Information

The video will progress at its own pace.

Do not attempt to speed up the video.

The post-test will only unlock after viewing the entire video.

The video can be paused and resumed later.
Course Objectives

After completing this module, participants should be able to...

- Identify three complementary and alternative (CAM) modalities that are effective for treating chronic pain.
- List three dietary supplements that are effective for treating osteoarthritis.
- Describe how prophylactic non-opioid treatment can prevent central and peripheral sensitization.
- Compare and contrast the synergistic effects of COX-1 and COX-2 inhibitors on pain.
Complementary and Alternative Therapies for Pain

Adriane Fugh-Berman MD
Georgetown University Medical Center
Collaborators

Milken Institute School of Public Health

THE GEORGE WASHINGTON UNIVERSITY

GEORGETOWN UNIVERSITY
Disclosure

Adriane Fugh-Berman MD has no commercial conflicts of interest. She directs PharmedOut, a Georgetown University Medical Center project that encourages rational prescribing. PharmedOut has a contract with the George Washington Milken Institute School of Public Health to create content for the DCDOH DC Center for Rational Prescribing (DCRx). She also has a contract with the George Washington Milken Institute School of Public Health to analyze pharmaceutical marketing data from Washington, DC. Dr. Fugh-Berman is a paid expert witness at the request of plaintiffs in litigation regarding pharmaceutical marketing practices. She is the author of two books on complementary medicine: The 5-Minute Herb and Dietary Supplement Consult (Lippincott, Wilkins and Wilkins, 2003) and Alternative Medicine: What Works (Odonion Press, 1996, out of print).
COCAINETOOTHACHE DROPS
Instantaneous Cure!
PRICE 15 CENTS.
Prepared by the
LLOYD MANUFACTURING CO.
219 HUDSON AVE., ALBANY, N. Y.
For sale by all Druggists.
(Registered March 1885.) See other side.

Cocaine was a common ingredient in many patent medicines, including those given to children. National Library of Medicine.
CAM Therapies for Pain

- Exercise
- Spinal manipulative therapy
- Acupuncture
- Yoga
- Herbs and dietary supplements
Pain and Suffering

• Pain is the physical sensation.
• Suffering includes the entire human experience of pain.
  • Varies among individuals
  • Encompasses depression, anxiety, fear, dread, frustration, anger, insomnia, etc.
Exercise and Osteoarthritis: Cochrane Reviews

• Exercise helps osteoarthritis of the hip and knee. Fransen 2014, Fransen 2015

• Another meta-analysis confirms benefits on hip OA. Sampath 2015

• Effects of exercise are comparable to NSAIDs for knee OA. Fransen 2015

• Effects on osteoarthritis of the hand are small and clinical relevance is debatable. Østerås 2017

• Aquatic exercise has clinically relevant effects on pain, disability, and QoL in people with knee and hip OA. Bartels 2016
http://www.cochranelibrary.com/
Exercise and Pain

• A comprehensive overview of 10 Cochrane reviews, 4 guidelines and 3 policy documents found that
  • Strong evidence supports exercise for neck, shoulder, knee, back and multi-site pain; exercise also improved function and QoL
    • In general, no particular exercise was superior
    • in patients with multisite pain, aerobic exercise was best

Babatunde 2017
Pilates and LBP

- A Cochrane systematic review of 10 trials found some evidence for the effectiveness of Pilates for low back pain
  - No conclusive evidence that it is superior to other forms of exercise

Yamato 2015
A 12-week single-blind RCT trial (n=320) adults with nonspecific LBP

- Compared 12 weekly yoga classes, 15 PT visits, or an educational book and newsletters.
- 40 week maintenance: yoga drop-in classes or PT booster sessions (both versus home practice)

Yoga was noninferior to PT for function and pain

Higher dropout rate in the PT group

Saper 2017
Yoga for LBP: Cochrane Review

- 12 trials (n=1,080)
- Compared to non-exercise controls, yoga results in small to moderate improvements in back-related function, and possibly pain, at 3 and 6 months.
  - Unclear whether yoga is superior to other exercise for back-related function or pain.

Wieland 2017
## Spinal Manipulative Therapy

<table>
<thead>
<tr>
<th>OSTEOPATHY</th>
<th>CHIROPRACTIC</th>
</tr>
</thead>
</table>
| Considered renegade until after WWII, now conventional | Licensed in all states  
Covered by Medicare and most insurance  
More than 160 million visits annually (one third of all visits to CAM practitioners) |
Osteopathic Manipulative Therapy: Low Back Pain

A systematic review of 15 studies of studies of OMT (10 for nonspecific LBP, 3 for LBP in pregnant women, 2 for LBP) in postpartum women found that OMT was superior to control interventions for pain and functional status for LBP in all groups.

Franke 2014
SMT for acute LBP

A Cochrane systematic review of 20 RCTs (n=2,674) found no benefit of SMT for acute low-back pain over controls (inert interventions, sham SMT, or as an adjunct to another invention).

Rubenstein 2012
A recent systematic review and meta-analysis of SMT for acute LBP (<6 weeks) found that SMT significantly improved function (12 RCTs, n=1381 patients, moderate evidence).

SMT significantly improved pain (15 RCTs, n=1711, moderate evidence).

No serious adverse events were reported.

Minor transient adverse events (increased pain, muscle stiffness, headache) were common.
Spinal Manipulation for Neck Pain

- A Cochrane systematic review of 51 trials (n=2,920) found benefits of thoracic manipulation versus control for neck pain, function, and QoL.

- Results for cervical manipulation and mobilization versus control are unclear.
  - Multiple cervical manipulation sessions may provide better pain relief and function improvement than some drugs.

Gross 2015
Chiropractic Care and Stroke

A large case-crossover study of all incident cases of carotid artery stroke admitted to hospitals in Ontario over 9 years (15,523) found no excess risk of carotid artery stroke after chiropractic care.

- No association of chiropractic care and stroke in patients over 45.
- For patients under 45, positive associations were seen for both visits to chiropractors and PCPs.
  - Most likely due to patients with neck pain or headache (early dissection-related symptoms) seeking care before developing stroke.

Cassidy 2017
That's odd... my neck suddenly feels better...

Early Acupuncture
Acupuncture for Pain

- Systematic reviews have shown that acupuncture was effective for pain associated with
  - Fibromyalgia *Deare 2013*
  - TMD *Fernandes 2017*
  - Herpes zoster (with moxibustion) *Coyle 2017*
  - Endometriosis *Xu 2017*
  - Post-stroke shoulder pain *Wu 2010*
Ear Acupuncture

A systematic review of 10 trials found that ear acupuncture was effective for immediate pain relief.
A Cochrane systematic review of 5 RCTs (n=285) found that:

1. Acupuncture benefited pancreatic cancer pain and late stage unspecific cancer

2. Auricular (ear) acupuncture was superior to placebo for chronic neuropathic pain

3. Acupuncture was equivalent to conventional analgesia for stomach carcinoma

4. No difference between real and sham acupuncture for ovarian cancer

Paley 2015
A Cochrane review of 15 studies (n=1,724) found that:

1. An analysis of 5 studies of TENS v. sham TENS found some benefit for TENS
2. Studies that compared TENS to usual care did not favor TENS
3. Quality of evidence was low

Gibson 2017
Psychological Interventions for Pain

A Cochrane review found benefits of psychological therapies for both chronic and recurrent pain in children and adolescents.

Another Cochrane review found that cognitive behavioral therapy (CBT)
- improved pain briefly (but not at follow-up)
- improved mood
- had a small effect on disability

Eccleston 2014

Williams 2012
Dietary Supplements for Pain

- Chondroitin
- Ginger
- Alpha-lipoic acid
- Carnitine
- White willow
- Glucosamine
- Capsaicin
Glucosamine and Chondroitin for Arthritis

Glucosamine, a small molecule found in meat (especially skin), is important in the formation of glycoproteins and connective tissue

• Commercially derived from chitin.

Chondroitin is a glycosaminoglycan found in cartilage

• Chondroitin is expensive.
• Bioavailability may vary with gut microbiota.

Shang 2016
Chondroitin appears to be more effective than glucosamine for pain

- A Cochrane review identified 43 RCTs of chondroitin in >9,000 subjects with osteoarthritis
  - Absolute difference in risk of pain was 9%-10% lower in chondroitin-treated subjects (<6 months)
  - Treatment significantly improved Lequesne’s index (pain, function and disability); absolute difference was 8%
- No serious adverse events were reported

Singh 2015
Chondroitin and Glucosamine: Mixed Results

GAIT, the largest trial, randomized 1,583 patients with knee OA to glucosamine 1500 mg, chondroitin 1200 mg, chondroitin plus glucosamine, celecoxib 200 mg, or placebo for 24 weeks.

- Overall, only celecoxib was better than placebo for pain.
  - Place response was 60%.
- For those with moderate-severe pain at baseline, combined therapy was superior. *Clegg 2006*

A recent trial of glucosamine and chondroitin for 6 months in 164 patients found no benefit over placebo. *Roman-Bias 2017*

Another study of 606 patients with knee osteoarthritis found that chondroitin plus glucosamine was as effective as celecoxib 200 mg. *Hochberg 2016*
Chondroitin, Glucosamine, and Prevention of Progression of Knee OA

• A systematic review found that chondroitin sulfate, compared to placebo, significantly reduced cartilage loss in 3 of 4 studies.

• Two of 3 glucosamine trials showed significant structural benefits compared to placebo. *Gallagher 2014*

• An observational study of 600 patients found that those who took glucosamine plus chondroitin had less cartilage loss over 2 years. *Martel-Pelletier 2015*
Adverse Events

• No serious adverse events have been reported in clinical trials of chondroitin or glucosamine.
  • An analysis of more than 3,000 patients found that glucosamine
    • Does not affect glucose levels in general.
    • May slightly decrease FBG levels after 66 weeks. Anderson 2005
  • Three cases of jaundice, cholestasis, or elevated liver enzymes have been reported in association with glucosamine/chondroitin supplements. Ip 2015
Carnitine for Peripheral Neuropathy

A systematic review of 4 RCTs (n=523) found that acetyl-carnitine significantly reduced pain scores of patients with peripheral neuropathy (especially diabetic neuropathy).

Li 2015
Alpha-Lipoic Acid (ALA) for Diabetic Peripheral Neuropathy

• ALA: A systematic review of 15 trials of alpha-lipoic acid (300-600 mg/day i.v.) found ALA superior to placebo for nerve conduction test and symptoms. *Han 2012*

• ALA may slow progression of neuropathy. *Ziegler 2011*

• A meta-analysis found that ALA and vitamin B<sub>12</sub> together were more effective than each separately. *Xu 2013*
ALA for Diabetic Neuropathy: Oral Use

- ALA (600 mg p.o. q.d.) in 460 patients for 4 years did not improve a composite score (the primary outcome) but did significantly improve neuropathy impairment and muscle weakness in the lower limbs.

- Significantly fewer ALA-treated patients showed progression.

- The treatment was tolerable.
  - There was a question of possible heart arrhythmias.

Ziegler 2011
SAMe and Osteoarthritis

• A Cochrane systematic review of 4 trials of 656 patients found a small but significant difference on standardized mean differences for pain and function. *Rutjes 2009*

• A meta-analysis of 11 RCTs (2 placebo-controlled, 9 treatment-controlled) found no effect on pain, but a reduction in functional limitation.
  • SAMe was equivalent to NSAIDs and caused fewer adverse events. *Soeken 2002*
  • SAMe is expensive. $
Zingiberaceae

- Turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), and galangal (*Alpinia galanga*), all of the family Zingiberaceae, have anti-inflammatory qualities.

- Curcumin down-regulates nuclear factors (NF)-kB and cyclooxygenase 2 (Cox-2).

- Gingerol, zingerone, and other components modulate leukotriene and prostaglandin synthesis and inhibit NF-kB.
Ginger and Osteoarthritis

• Systematic reviews have shown a benefit of ginger extracts for pain. *Lakhan 2015, Terry 2011*

• Trials of curcumin, curcuminoids, and tumeric extract have also shown benefit.
  • No adjunct advantage of 1,000 mg curcumin/day over placebo when combined with diclofenac. *Lakhan 2015*
Ginger Compared with NSAIDs

- A systematic review and meta-analysis found ginger equivalent to NSAIDs for pain. *Lakhan 2015*

- In a placebo-controlled study of 67 adults, ginger was equivalent to ibuprofen for pain after surgery for an impacted molar. *Rayati 2017*

- In 112 women with moderate to severe dysmenorrhea, ginger (250 mg Zintona q 6 hr) was equivalent to mefenamic acid (250 mg q 8 hr) for dysmenorrhea. *Shirvani 2015*
Gingerols

- [6] gingerol and [8]-gingerol are agonists of the capsaicin-activated vanilloid receptor
- VR1 integrates chemical and thermal nociceptive stimuli
- Activation of VR1 is associated with analgesia
- Gingerols were less potent than capsaicin

Dedov 2002
Does ginger cause bleeding?

Although some components of ginger have antiplatelet qualities, in normal medicinal doses, ginger does not increase bleeding risk.
White Willow (*Salix alba*) Bark

- White willow bark (standardized to 120 mg or 240 mg) salicin improved pain short-term in 2 trials (n=261)
  - A low-quality trial showed equivalence to rofecoxib 12.5 mg/day. *Oltean 2014*

- White willow (240 mg *salicin*) had only a minimal effect on platelet thrombosis vs. ASA (100 mg) in 51 people
  - Mean maximal arachidonic acid induced platelet aggregation
    - 61% in the *Salix* group
    - 78% in the placebo group
    - 13% in the ASA group *Krivoy 2001*
Capsaicin cream

- Is sold OTC
- Usually 0.25% or 0.75% capsaicin
- Applied up to 4 times daily
- Wash hands after applying!
- Can cause burning, stinging, or itching, especially with initial use
Topical Capsaicin: RCTs

- *Capsicum frutescens* cream or plaster benefited people with chronic LBP (3 trials, n=755)
  - Unclear whether topical capsicum cream benefits acute LBP *Oltean 2014*

- Capsaicin cream also benefits
  - Diabetic neuropathy *Capsaicin Study Group 1991*
  - Post-mastectomy pain syndrome *Watson 1992*
  - Fibromyalgia *McCarty 1994*
Capsaicin

• A capsaicin dermal patch has been approved for treating post-herpetic neuralgia (30-60 minute application every 3 months).
  McCormack 2010

• Capsaicin selectively binds to a vanilloid receptor (transient receptor potential ion-TRPV1) common in pain-transmitting C fibers.

• Capsaicin depletes Substance P.
Summary

• Multiple RCTs support exercise or SAMe for osteoarthritis
• Chondroitin (and possibly glucosamine) may help forestall cartilage volume loss in OA
• It is unclear whether SMT, acupuncture, or TENS are more effective than sham interventions for pain
• Carnitine and ALA are helpful for peripheral neuropathy
• Ginger, capsaicin, and white willow are effective for pain
• CAM therapies have an important adjunct role to play in pain treatment
CONCLUSION

Evidence from multiple controlled trials supports exercise, SMT, carnitine, SAMe, ginger, and capsaicin for pain.

CAM therapies have an important adjunct role to play in pain treatment.
Do you have any experience with pulsed electromagnetic field therapy?
Would you advise someone with back pain to get spinal manipulative intervention before getting surgery?
Do you have any experience in the use of copper for joint pain?
It seems that SAMe has more evidence than acupuncture does, can you comment on that?
Pain Management with NSAIDs in the Opioid Overdose Era

Raymond Dionne
Eastern Carolina University
Raymond.dionne@icloud.com
**Conflict of Interest Statement:** The speaker is on the faculty of the ECU School of Dental Medicine and Brody School of Medicine, serves on the scientific advisory board of Charleston Laboratories and the Global Pain Faculty of GlaxoSmithKline and has consulted for the pharmaceutical industry in the past. He is also on the editorial board of the Compendium, Applied Clinical Pharmacology and Toxicology, and Clinical Pharmacology and Translational Medicine.

This presentation is approved by East Carolina University as an External Professional Activity for Pay #18-03728.
Therapeutic Objectives of Pain Management in Ambulatory Patients

- Efficacious pain relief
- Fast onset
- Minimal side effects
- Safety when used clinically
- Practical: OTC vs. Rx drugs
- Prevent sensitization leading to hyperalgesia at later time points
# Milestones in Understanding Pain and Improving Analgesics

## Major Drug Cases

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcotics</td>
<td>Opiates</td>
<td>Opioids</td>
<td>Opioids</td>
<td>Coxibs</td>
<td>NSAIDs</td>
<td>PRO's</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Aspirin</td>
<td>NSAIDs</td>
<td>NSAIDs</td>
<td>Antidepressants</td>
<td>Acetaminophen</td>
<td>Phenotyping</td>
</tr>
<tr>
<td>Adjuncts</td>
<td>Acetaminophen</td>
<td>Acetaminophen</td>
<td>Acetaminophen</td>
<td>Anticonvulsants</td>
<td>Adjuncts</td>
<td>Personalized</td>
</tr>
<tr>
<td></td>
<td>Adjuncts</td>
<td>Adjuncts</td>
<td>Adjuncts</td>
<td>Opioids</td>
<td>NSAIDs</td>
<td>medicine</td>
</tr>
</tbody>
</table>

## Milestones

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo response</td>
<td>Clinical trials methodology</td>
<td>Opiate receptor</td>
<td>Endogenous pain inhibitory system</td>
<td>Gender, Genetics Imaging</td>
<td>Pharmacogenomics Gene expression Proteomics Opioid OD epidemic</td>
<td></td>
</tr>
<tr>
<td>Category scales</td>
<td>Aspirin MOA Dental model</td>
<td>Aspirin MOA Dental model</td>
<td>Aspirin MOA Dental model</td>
<td>Aspirin MOA Dental model</td>
<td>Aspirin MOA Dental model</td>
<td></td>
</tr>
</tbody>
</table>

A NEJM 1980 Letter was used as justification for advocating widespread use of opioids for non-malignant pain: ‘despite the widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.’

Cited 608 times as evidence of safety | Washington Post June 2, 2017
Why Do We Prescribe Opioid Combinations?

Established prescribing behaviors

• Efficacy of APAP-opioids established in 1970’s, before NSAIDs introduced
• Improved clinical analgesic research (Cooper & Beaver 1976)
• NSAIDs efficacy and safety >> opioid combinations

Misperception of DEA scheduling of opioids

• Schedule 2 drugs have greater abuse potential, not efficacy

Placebo response contribution to analgesic efficacy

• Placebo pills are effective 10-20% of the time in clinical pain trials
• Misperception that Rx analgesics are more potent than OTC analgesics
Why Do We Prescribe Opioid Combinations?

Prescribing for most severe outcome
- Often prescribe to manage the worse case scenario
- May benefit 20% with worse pain, but not needed for the other 80%

Unfounded expectations of APAP efficacy
- Maximum dose reduced from 1000 mg to 650 mg

Patient expectations and demands
- Not providing an opioid can be perceived as less than optimal treatment

Moore 2016
Little additive analgesic effect in combination with an NSAID

Dionne 1999
Preventing the Transition from Tissue Injury to Hyperalgesia

- Blocked by NSAIDs
- Minimizes
- Resulting in much less
- Produces little or no
- ‘Slight’ pain after LA offset, instead of

Tissue Injury → Local release of active factors. (PG, BK, K) → Persistent activation/sensitization of Aδ/C. → Activity in ascending pathways + spinal facilitation → Exaggerated output for given stimulus input → Ongoing pain + Hyperalgesia
Sensitization

- Occurs in periphery and CNS
- Results in increased pain to a given stimulus
- Manifests clinically as hyperalgesia or allodynia
- Can last beyond duration of tissue injury and repair

*Campbell and Meyer 1980*
Relationship Between Pain and PGE$_2$ Levels at the Site of Injury
Differentiation of Cyclooxygenase Inhibition for Pain

Anesthetic Offset

Inflammatory Response

Nociceptive Input

Pain Onset

Moderate Pain

Sensitization

Surgical Extractions 2-4 Third Molars

1

2

3

n

24

48

Hours

Pre- or Post-op

Analgesics

Single or Multiple Dose

Sample collection: (eg, blood, tissue, etc)
Toxicity Limits Increasing NSAID Dose

- COX2 cardiovascular risk might only be due to rofecoxib. 
  *Gunther 2017*

- All NSAIDs, including naproxen, were associated with an increased risk of acute MI. 
  *Bally 2017*

- The cardiovascular risk of popular analgesics is still unclear ("this study was anything but PRECISION"). 
  *American Heart Association 2017*
Treating pain before it starts reduces peripheral sensitization.
Measurement of PGE$_2$ and TBXB$_4$ as Biomarkers for COX inhibition

Impacted Third Molars

PAIN
Representative RT-PCR Products

Preoperative Biopsy Site

Postoperative Biopsy Site

<table>
<thead>
<tr>
<th></th>
<th>Pre 30min</th>
<th>Pre 60min</th>
<th>Pre 120min</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td>388bp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2</td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td>275bp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3PDH</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
</tr>
<tr>
<td>167bp</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Khan 2002
Differential Time Course of COX-1 and COX-2 Products

![Graph showing the time course of PGE2 production after surgery with Placebo, COX-2 inhibitor, and COX-1/COX-2 inhibitor.](image-url)
Central Sensitization: Due to Postoperative Pain Input

Anesthetic Offset

Nociceptive Input

Surgical Extractions 2-4 Third Molars

Pain Onset

1 2 3 n

Acute Pain

Inflammatory Response

Sensitization

24 48

975 mg Acetaminophen PRN

Lidocaine or saline

Bupivacaine or saline

Plasma ß-endorphin (RIA)
Contribution of COX-1 and COX-2 to Acute Inflammation
NSAID Suppression of COX-2

Time Post-Surgery (mins)

i.r. Prostaglandin E2 (pg/mL)

Placebo

Celecoxib

Ibuprofen

Khan 2002
Preventive Effects of Postop Pain Control

Immediate Postop. Pain

Pain at 48 Hours

* P < 0.001 Bupivacaine drug effect, 2-ANOVA

* P < 0.05 Bupivacaine drug effect, 2-ANOVA
COX-1 vs. COX-2 as Analgesic Targets

Expression Level (log2)

COX-1

- Pre-surgery
- 4 hours placebo
- 48 hours placebo
- 48 hours ibuprofen
- 48 hours rofecoxib

COX-2

Fold Change

* indicates statistical significance.
Changes in inflammatory gene expression acutely

Phase 1 Analysis 2006
Dual COX-1/COX-2 Suppression Prevents Central Sensitization

Pain Postoperatively

Pain at 24 and 48 hr
Toxicity of NSAIDs are based on their Selectivity for COX1 or COX2.
Adverse effects
GI/Cardiovascular Toxicity
Acetaminophen Mechanism of Action

- Inhibits prostaglandin hydroperoxidase
- Blocks COX-2
- Metabolites of acetaminophen act on TRPA1-receptors in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain.
- One metabolite (AM-404) inhibits sodium channels and the reuptake of endogenous cannabinoids.
Is Acetaminophen a COX-2 Inhibitor?

![Graph showing PGE$_2$ (pg/mL) vs. Time Post-Surgery (min) for placebo, acetaminophen*, rofecoxib*, and ketorolac*]
Strategies for Preventive Analgesia: Reduce Nociceptive Barrage with an NSAID and a Long-Acting Local Anesthetic

Dionne 1984
PAIN Management Paradigm

- P = Prevention
- A = Anti-inflammatory agents, Acetaminophen, Anesthetics
- I = Individualize
- N = Narcotics (opioids)

- Opioid prescriptions should be written only to supplement the analgesic effects of NSAIDs or APAP
- Opioid prescriptions should be written with discretion
- In general, *refills for acute pain medication*, especially those containing an opioid, should be avoided.
Prescribing options for acute pain to minimize opioid misuse or abuse

MILD PAIN
OTC ibuprofen, naproxen or ketoprofen as needed

MILD TO MODERATE PAIN
Ibuprofen 400-600 mg every 4-6 hours by the clock for first 48-72 hours, not to exceed maximum recommended daily dose. As needed until pain subsides

MODERATELY SEVERE PAIN
Prescription dose of NSAID administered prior to the procedure or immediately afterwards

Administration of long-acting local anesthetic 0.5% bupivacaine with epinephrine for procedural anesthesia and postoperative analgesia

Postoperative administration of prescription dose of NSAID administered by the clock for 48-72 hours combined with administration of acetaminophen 600/650 mg by the clock; the two medications can be given concurrently or alternated to maintain blood levels of both medications

Moderately Severe Pain

- Provide a prescription of an opioid drug in combination with acetaminophen to be filled and administered only if needed for pain not relieved by regimen for moderately severe pain.
  - EXAMPLE: 2 tablets of 325 mg acetaminophen plus 37.5 mg tramadol every 4-6 hours for pain, not to exceed 8 tablets every 24 hours
- Note: Separate dosing of 600/650 mg acetaminophen should be discontinued.

Dionne 2016
Comparison of Conventional Approach to Targeted Strategies

<table>
<thead>
<tr>
<th>Relative Effects of Treatment</th>
<th>Opioid Combinations</th>
<th>Preventive/Additive/Adaptive Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Abuse Potential</td>
<td>+++</td>
<td>none (without opioid) + (with tramadol) ++ (with oxycodone or hydrocodone)</td>
</tr>
<tr>
<td>Overdose Risk</td>
<td>++</td>
<td>none (without opioid) + (with tramadol) ++ (with oxycodone or hydrocodone)</td>
</tr>
</tbody>
</table>

Relative effects based on well-established pharmacology of drug classes and specific agents ranked on a scale from none to +++

<table>
<thead>
<tr>
<th>DRUG CLASS (REPRESENTATIVE AGENTS IN PARENTHESES)</th>
<th>DRUG ACTION</th>
<th>SITE OF ACTION&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RELATIVE EFFICACY IN PAIN STATES&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs (ibuprofen, aspirin, acetaminophen)</td>
<td>Nonspecific COX inhibitors</td>
<td>Peripheral and spinal</td>
<td>Tissue injury &gt;&gt; acute stimuli = nerve injury = 0 (Hamza and Dionne, 2009, Svensson and Yaksh, 2002)</td>
</tr>
<tr>
<td>COX 2 inhibitor (celecoxib)</td>
<td>COX2-selective inhibitor</td>
<td>Peripheral and spinal</td>
<td>Tissue injury &gt;&gt; acute stimuli = nerve injury = 0 (Hamza and Dionne, 2009)</td>
</tr>
<tr>
<td>Opioids (morphine)</td>
<td>μ receptor agonist</td>
<td>Supraspinal and spinal</td>
<td>Tissue injury = acute stimuli ≥ nerve injury &gt; 0 (see this chapter)</td>
</tr>
<tr>
<td>Anticonvulsants (gabapentin)</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; channel block, α&lt;sub&gt;2&lt;/sub&gt;δ subunit of Ca&lt;sup&gt;2+&lt;/sup&gt; channel</td>
<td>Supraspinal and spinal</td>
<td>Nerve injury &gt; tissue injury = acute stimuli = 0 (Lai et al., 2004; Taylor, 2009)</td>
</tr>
<tr>
<td>Tricyclic antidepressants (amitryptiline)</td>
<td>Inhibit uptake of 5-HT/NE</td>
<td>Supraspinal and spinal</td>
<td>Nerve injury ≥ tissue injury &gt;&gt; acute stimuli = 0 (Mochizucki, 2004)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Studies based on local delivery in preclinical models, e.g., intracranial microinjection or intraventricular injections, lumbar intrathecal delivery or topical/sq application at injury site. <sup>b</sup>Pain states are defined by preclinical models: acute: hot plate/tail flick/acute mechanical compression; tissue injury: intraplantar injections of irritants, focal thermal injury; nerve injury: compression/ligation of sciatic nerve or its branches or of nerve roots; systemic delivery of chemotherapeutics. See Mogil, 2009.
Opioid Prescribing Recommendations Revisited

• Assess medical and drug histories.
• Communicate with patients.
• **Limit the quantity of opioid analgesics prescribed.**
• Inform patients not to share medications.
• Alert adolescent patients/parents to abuse potential.
• Educate parents about secure medication storage.
• Dispose of unused prescription medications.
• **Consider alternative strategies for pain control.**
A criticism of opioid use is that there is no long-term data, is there long-term data on NSAID use?
From a pharmacology standpoint, what if the cut-off for level of kidney function paired with cannabis versus NSAID use?
How did you interpret the study in BMJ this year which was a meta-analysis on NSAIDs that showed an increase in myocardial infarction across the board?
More resources available at the DC Center for Rational Prescribing
doh.dc.gov/dcrx
DCRx Modules

- Tight Control in Type 2 Diabetes: More Harm Than Good?
- Taking a Sexual History to Reduce HIV Risk
- Myths and Facts about Opioids
- Medical Cannabis: An Introduction to the Biochemistry & Pharmacology
- Medical Cannabis: Evidence on Efficacy
- Medical Cannabis: Adverse Effects and Drug Interactions
- Industry Influence on the Practice of Medicine
- What You Need to Know about PrEP
- Getting Patients Off of Opioids
- Rational Prescribing in Older Adults
- Drug Approval and Promotion in the United States
- Generic Drugs: Myths and Facts