Non-Opioid and Alternative Approaches for Pain

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More resources available at the
DC Center for Rational Prescribing

doh.dc.gov/dcrx

Course Faculty

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- Susan Wood, PhD

Important Information

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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

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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

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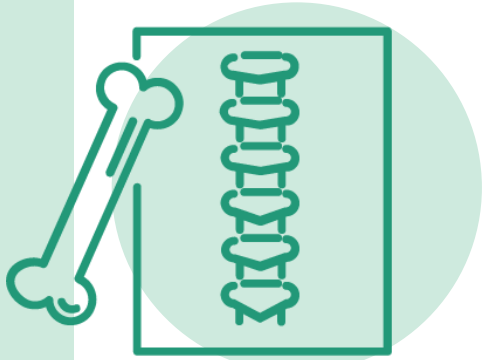

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Disclosure

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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).

COCAINE
TOOTHACHE 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.

3. Cocaine was a common ingredient in many patent medicines, including those given to children. *National Library of Medicine.*

CAM Therapies for Pain

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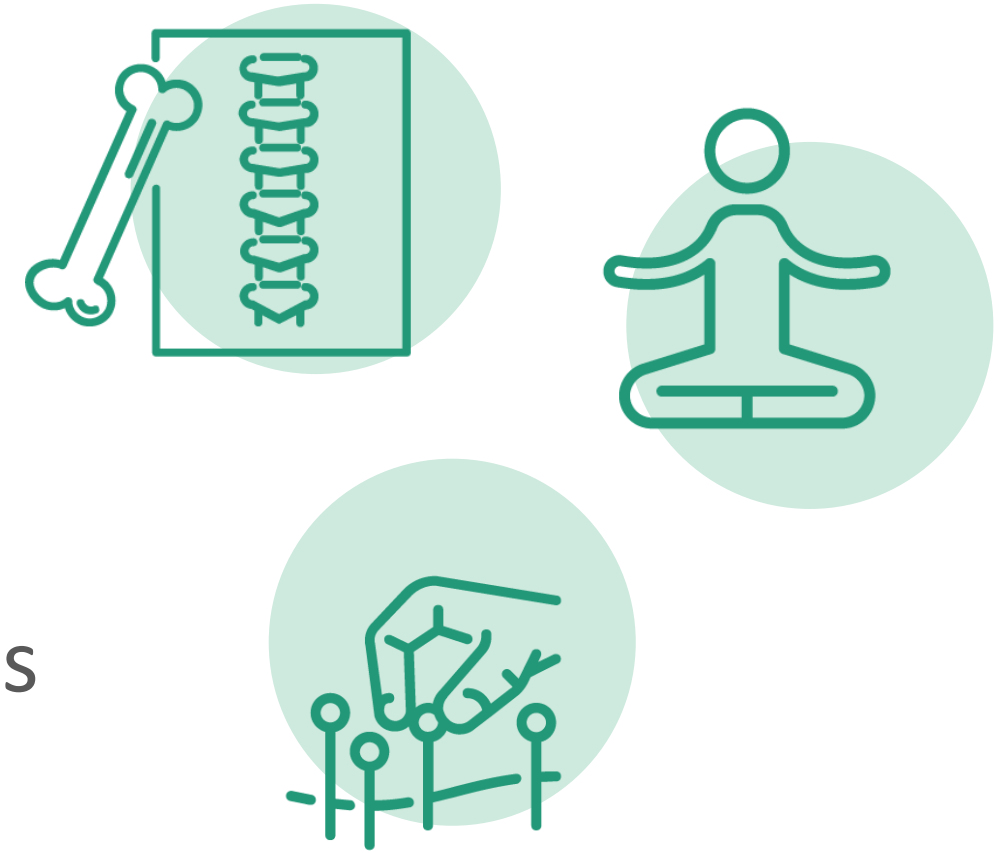
- Exercise
- Spinal manipulative therapy
- Acupuncture
- Yoga
- Herbs and dietary supplements



Pain and Suffering

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- 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

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- 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*

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Cochrane

http://www.cochranelibrary.com/

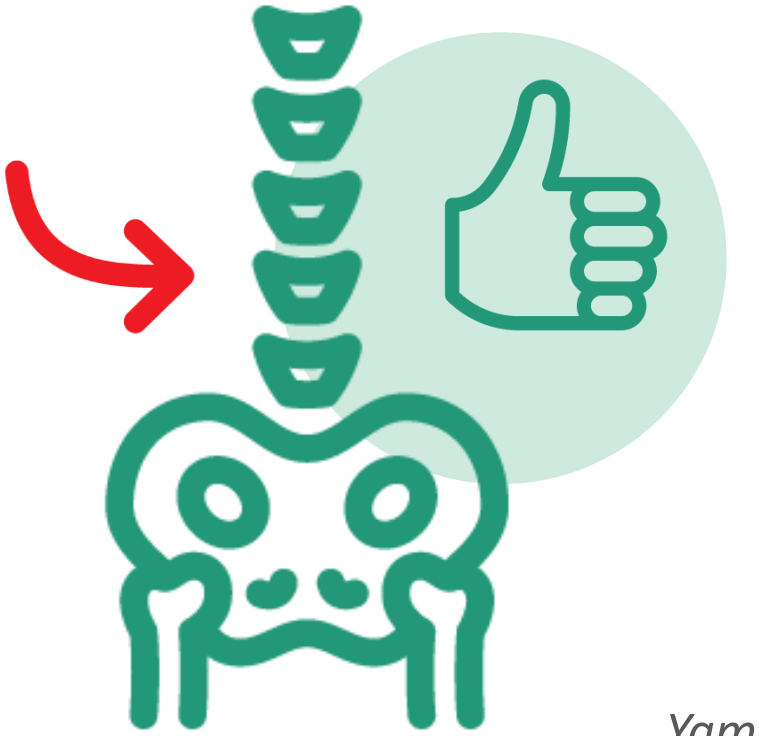
Exercise and Pain

- 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

Yoga vs. PT for LBP

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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

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- 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

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OSTEOPATHY

Considered renegade until after WWII, now conventional

CHIROPRACTIC

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

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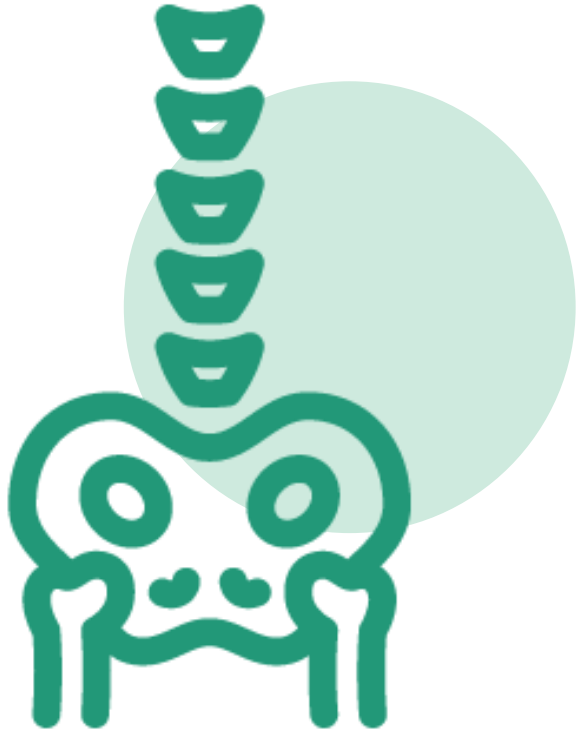
A Cochrane systematic review of 20 RCTs (n=2,674) found no benefit of SMT for acute low-back pain over controls (inert interventions, sham SMT, or as an adjunct to another invention).



Rubenstein 2012

SMT for acute LBP

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A recent systematic review and meta-analysis of SMT for acute LBP (<6 weeks) found that

Paige 2017

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

SMT significantly improved function (12 RCTs, n=1381 patients, moderate evidence).

No serious adverse events were reported.

Minor transient adverse events (increased pain, muscle stiffness, headache) were common.

Spinal Manipulation for Neck Pain

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- 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

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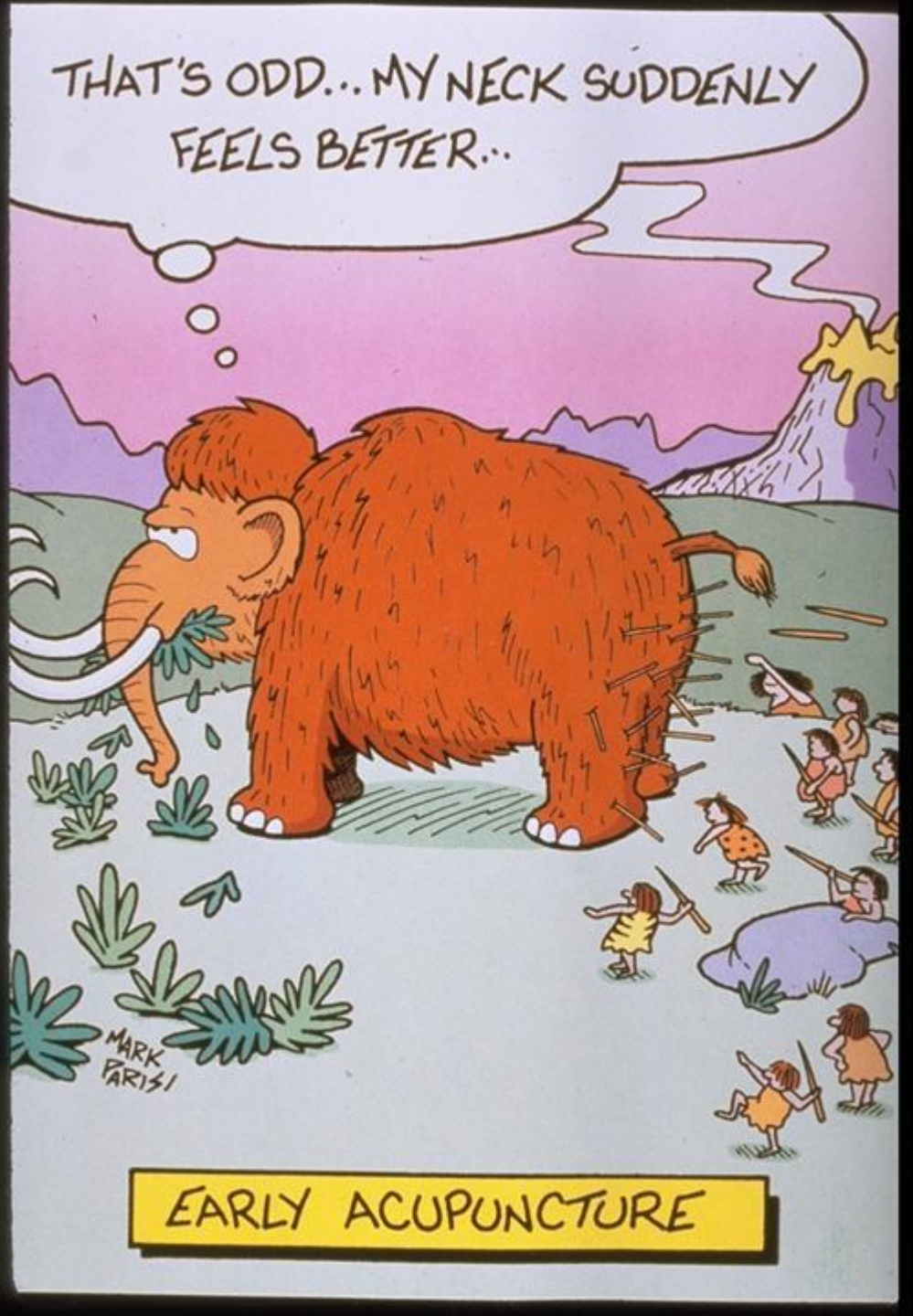
A large case-crossover study of all incident cases of carotid artery stroke admitted to hospitals in Ontario over 9 years (15,523) found no excess risk of carotid artery stroke after chiropractic care.

- 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...
MARK PARISI
EARLY ACUPUNCTURE

Acupuncture for Pain

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- 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

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A systematic review of 10 trials found that ear acupuncture was effective for immediate pain relief.

Acupuncture and Cancer Pain

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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

Transcutaneous Electrical Nerve Stimulation (TENS) for Neuropathic Pain

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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

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

Eccleston 2014

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

Williams 2012

Dietary Supplements for Pain

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- Chondroitin
- Ginger
- Alpha-lipoic acid
- Carnitine
- White willow
- Glucosamine
- Capsaicin

Glucosamine and Chondroitin for Arthritis

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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

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- 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

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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

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- 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

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- 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

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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

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- 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_{12} together were more effective than each separately. *Xu 2013*

ALA for Diabetic Neuropathy: Oral Use

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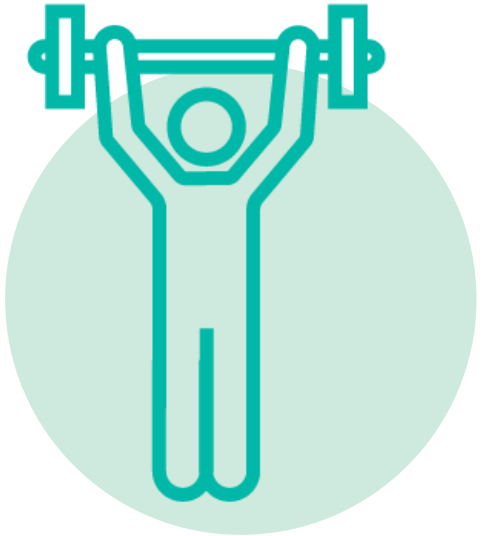
- ALA (600 mg p.o. q.d.) in 460 patients for 4 years did not improve a composite score (the primary outcome) but did significantly improve neuropathy impairment and muscle weakness in the lower limbs.
- Significantly fewer ALA-treated patients showed progression.
- The treatment was tolerable.
  - There 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

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- 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

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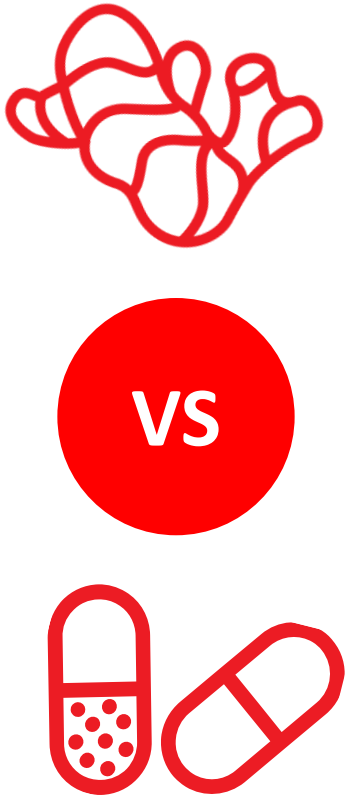
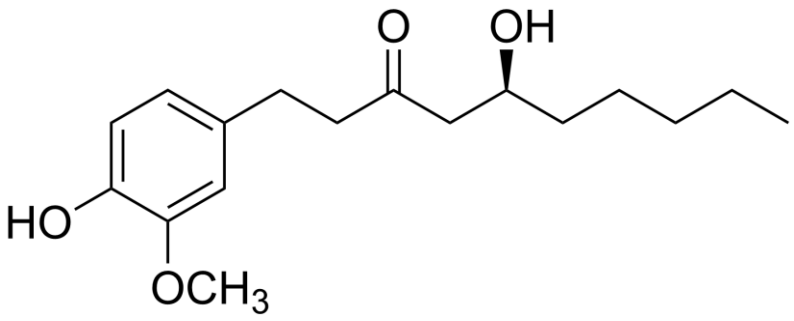
- A systematic review and meta-analysis found ginger equivalent to NSAIDs for pain. *Lakhan 2015*
- In a placebo-controlled study of 67 adults, ginger was equivalent to ibuprofen for pain after surgery for an impacted molar. *Rayati 2017*
- In 112 women with moderate to severe dysmenorrhea, ginger (250 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

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- 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

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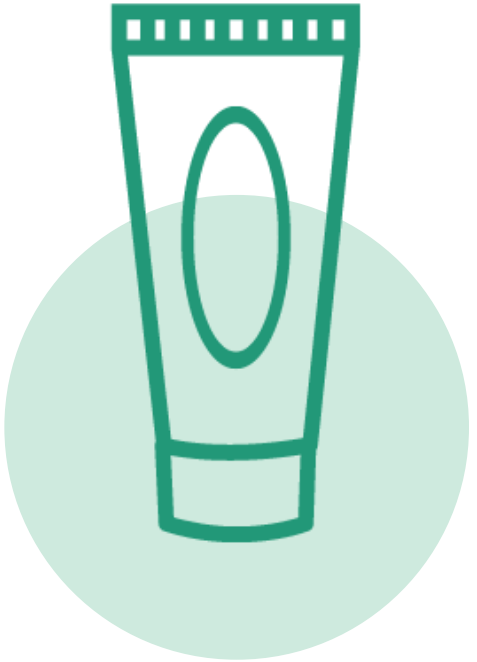
- *Capsicum frutescens* cream or plaster benefited people with chronic LBP (3 trials, n=755)
  - Unclear whether topical capsicum cream benefits acute LBP *Oltean 2014*
- Capsaicin cream also benefits
  - Diabetic neuropathy *Capsaicin Study Group 1991*
  - Post-mastectomy pain syndrome *Watson 1992*
  - Fibromyalgia *McCarty 1994*



Capsaicin

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- 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

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- 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.

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Do you have any experience with pulsed electromagnetic field therapy?

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Would you advise someone with back pain to get spinal manipulative intervention before getting surgery?

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Do you have any experience in the use of copper for joint pain?

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It seems that SAMe has more evidence than acupuncture does, can you comment on that?

Pain Management with NSAIDs in the Opioid Overdose Era

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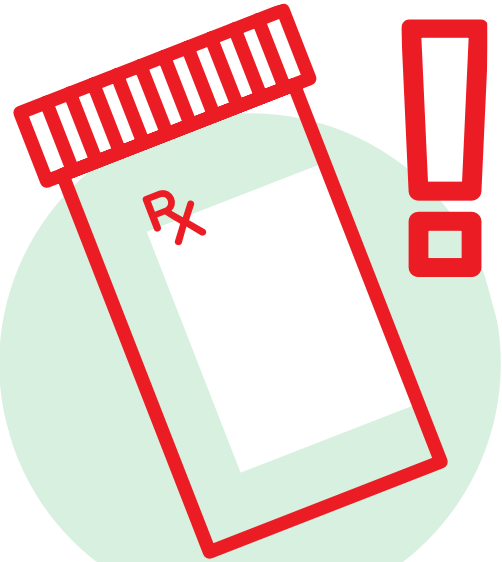

Conflicts of Interest

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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

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- 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

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	1950's	1960's	1970's	1980's	1990's	2000's	Beyond?
MAJOR DRUG CASES	• Narcotics • Aspirin • Adjuncts	• Opiates • Aspirin • Acetaminophen • Adjuncts	• Opioids • NSAIDs • Acetaminophen • Adjuncts	• Opioids • NSAIDs • Acetaminophen	• Coxibs • Antidepressants • Anticonvulsants • Opioids • NSAIDs • Acetaminophen	• NSAIDs • Acetaminophen • Opioids • Gabapentin	• PRO's • Phenotyping • Personalized • medicine
MILESTONES	Placebo response Category scales	Clinical trials methodology	Opiate receptor Aspirin MOA Dental model	Endogenous pain inhibitory system	Gender, Genetics Imaging	Pharmacogenomics Gene expression Proteomics Opioid OD epidemic	

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?

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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?

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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

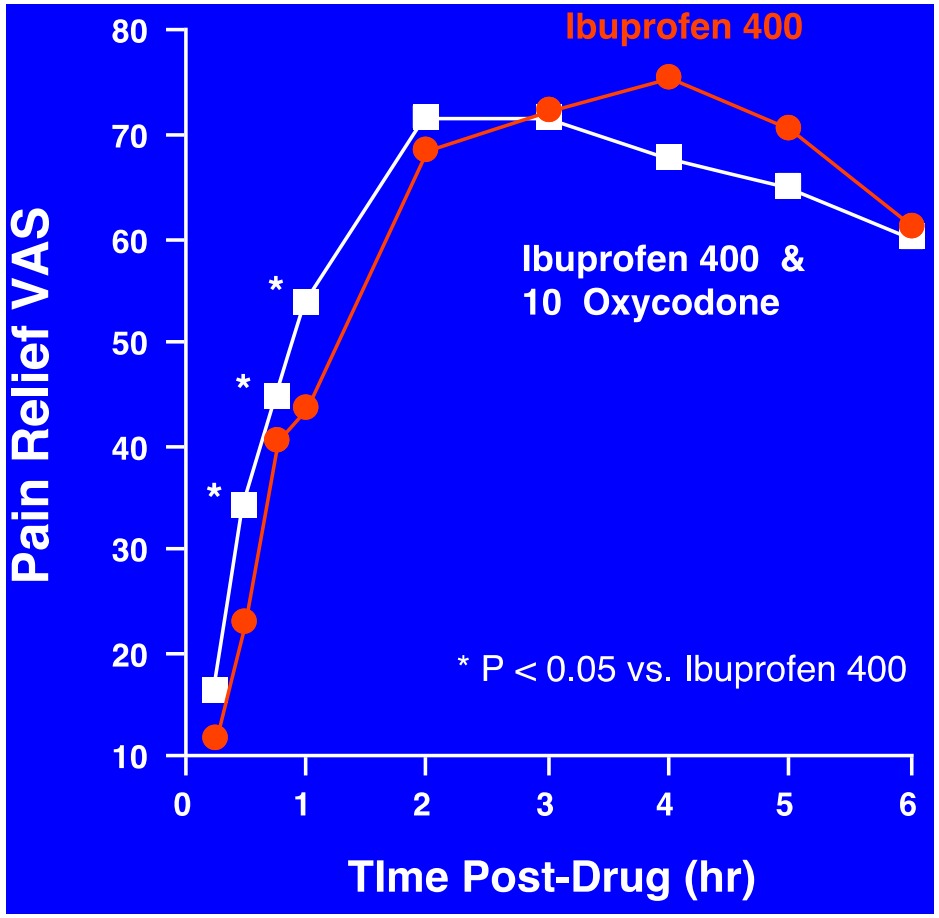
- Maximum dose reduced from 1000 mg to 650 mg

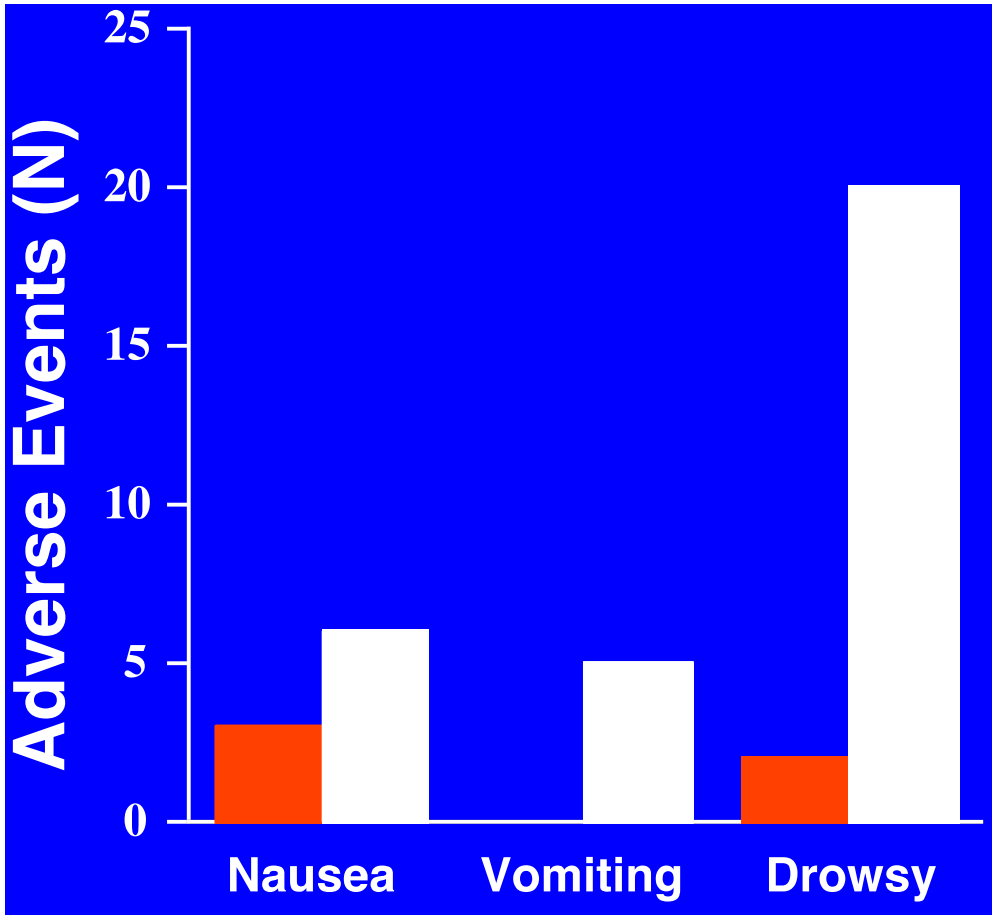
Patient expectations and demands

- Not providing an opioid can be perceived as less than optimal treatment

Moore 2016

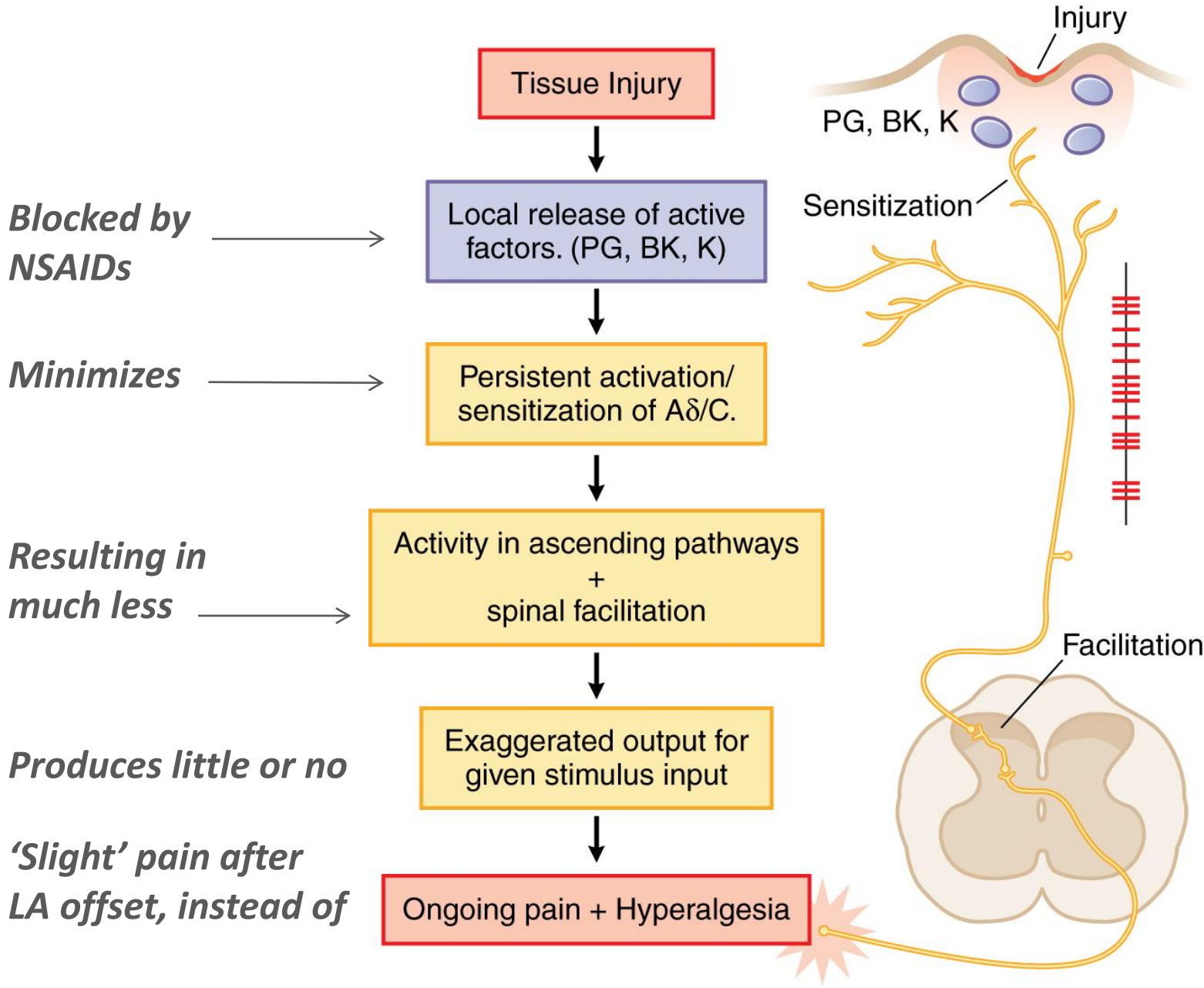
Little additive analgesic effect in combination with an NSAID





Dionne 1999

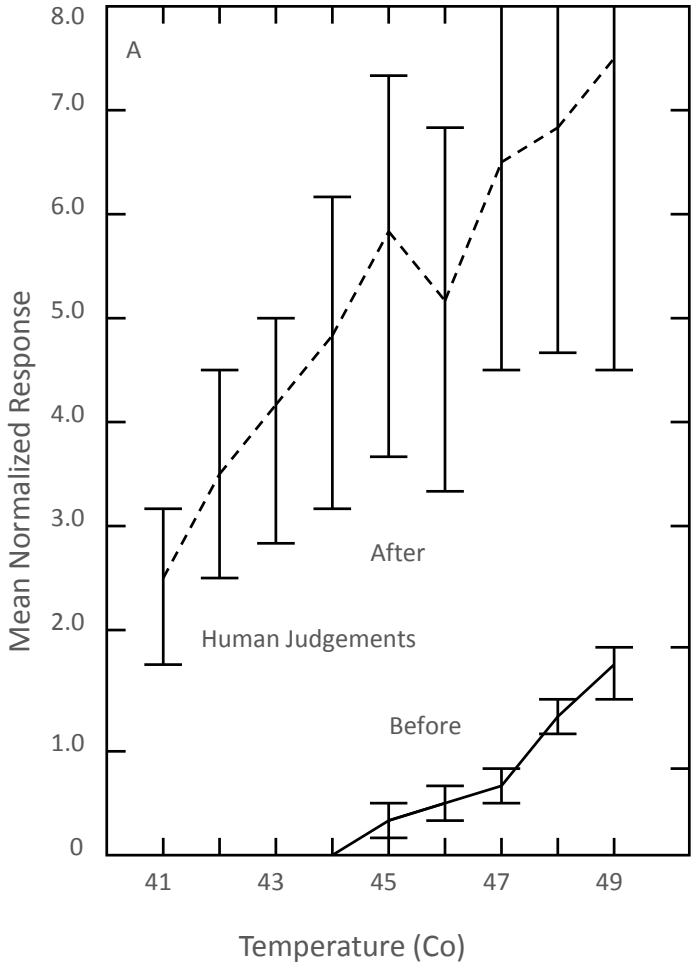
Preventing the Transition from Tissue Injury to Hyperalgesia



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

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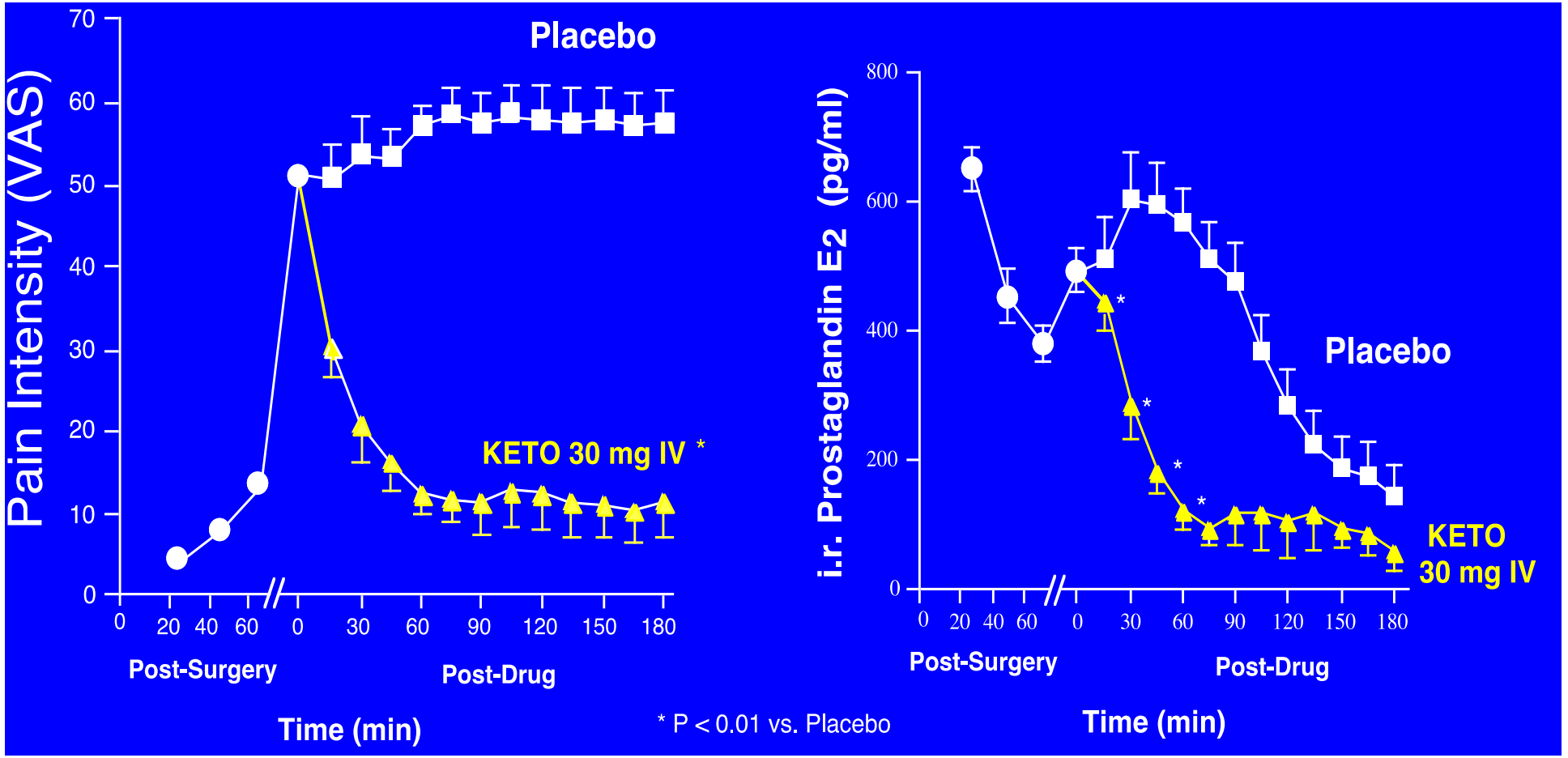

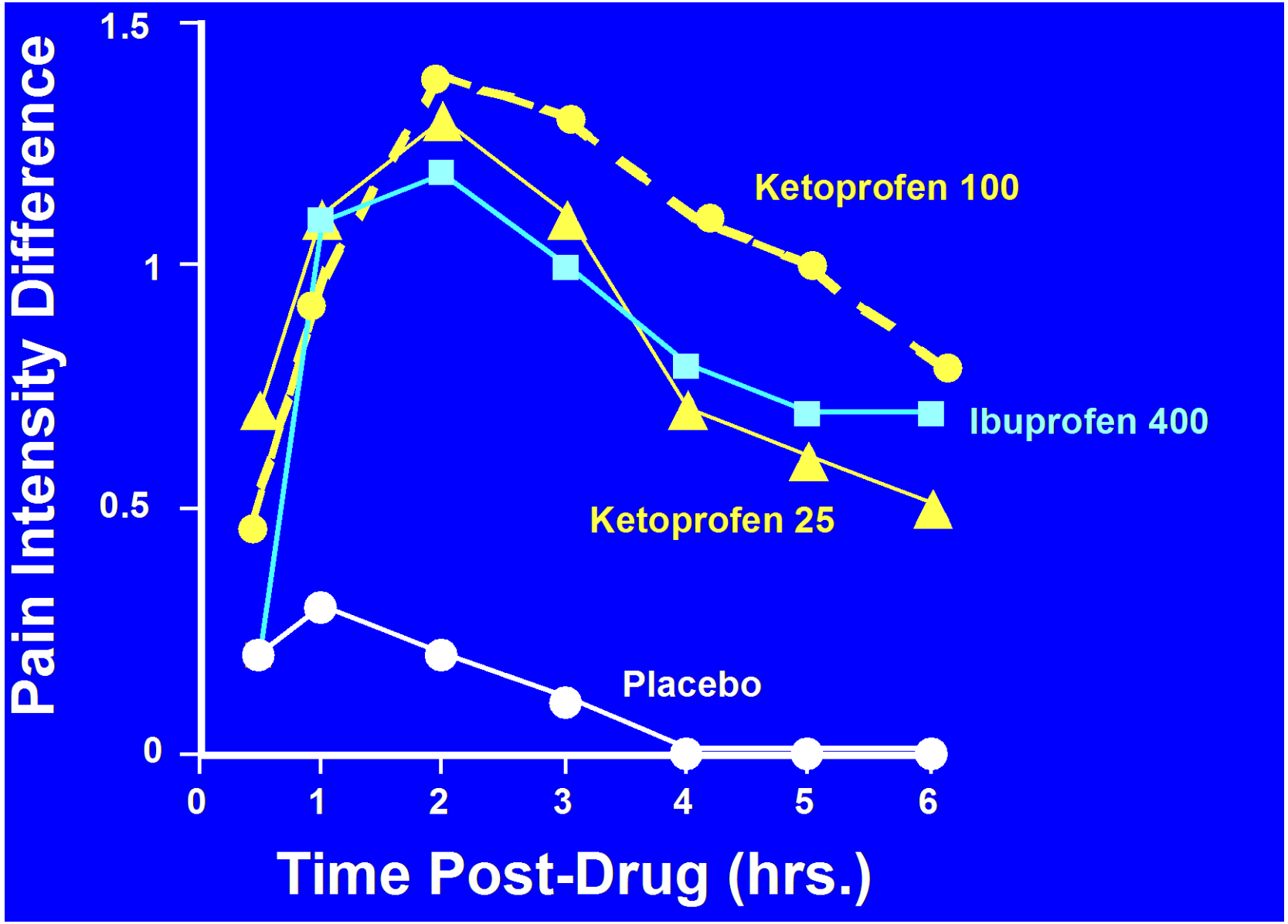

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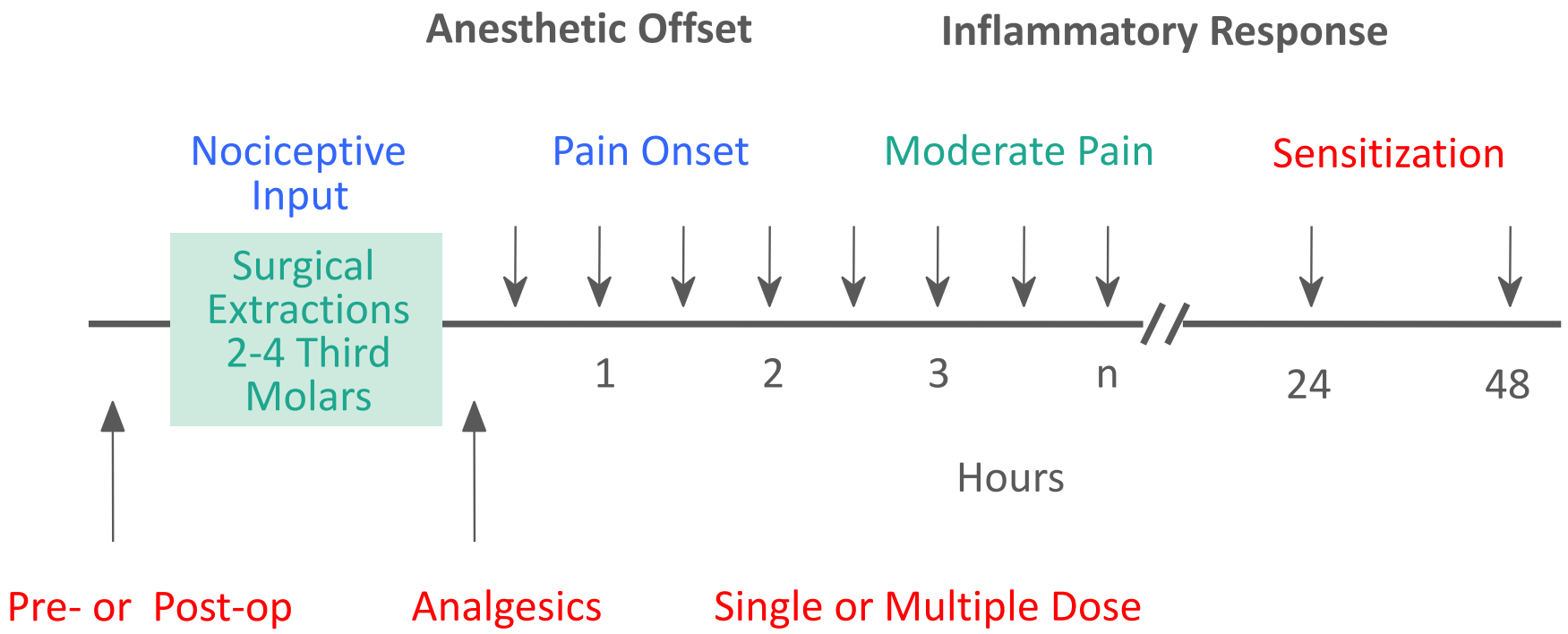
Differentiation of Cyclooxygenase Inhibition for Pain



Sample collection: (eg, blood, tissue, etc)

Toxicity Limits Increasing NSAID Dose

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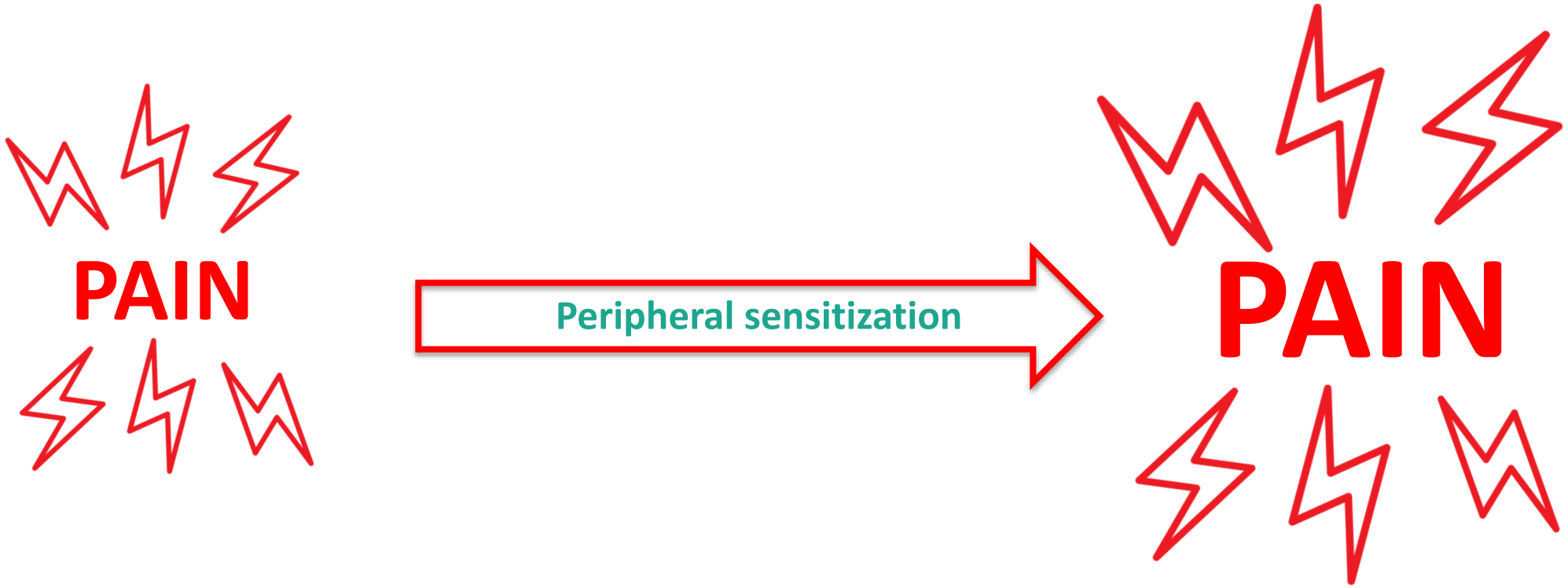
- COX2 cardiovascular risk might only be due to rofecoxib.
  Gunther 2017
- All NSAIDs, including naproxen, were associated with an increased risk of acute MI.
  Bally 2017
- The cardiovascular risk of popular analgesics is still unclear ("this study was anything but PRECISION").
  American Heart Association 2017

Treating pain before it starts reduces peripheral sensitization.



Measurement of PGE_2 and $TBXB_4$ as Biomarkers for COX inhibition

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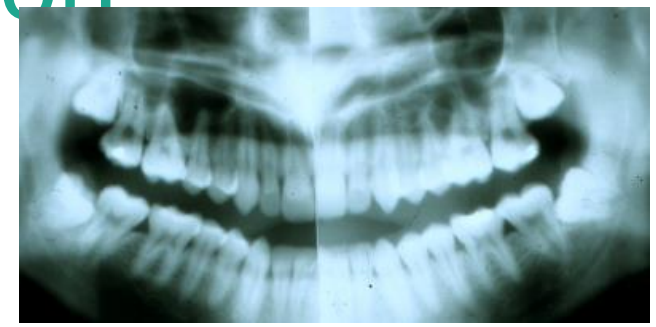
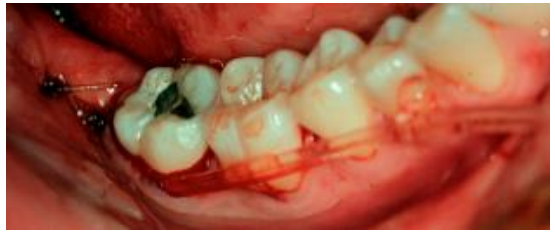
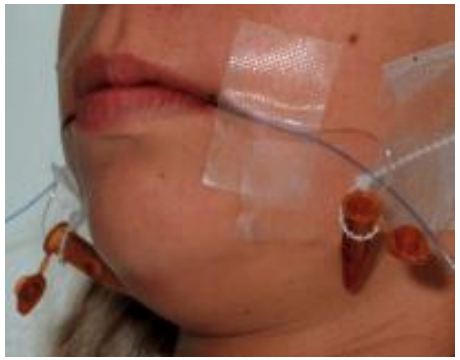
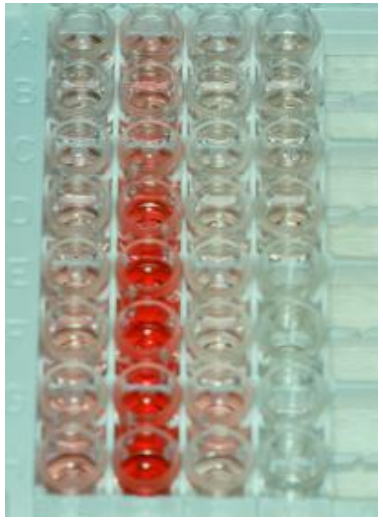
Impacted Third Molars







PAIN



Representative RT-PCR Products

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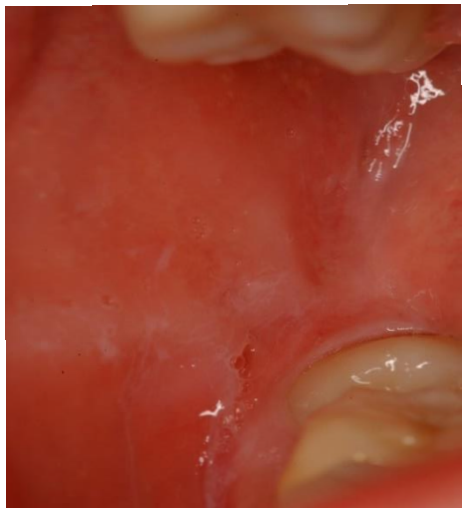
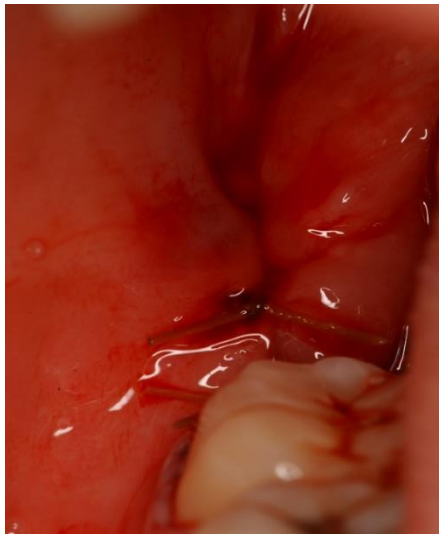
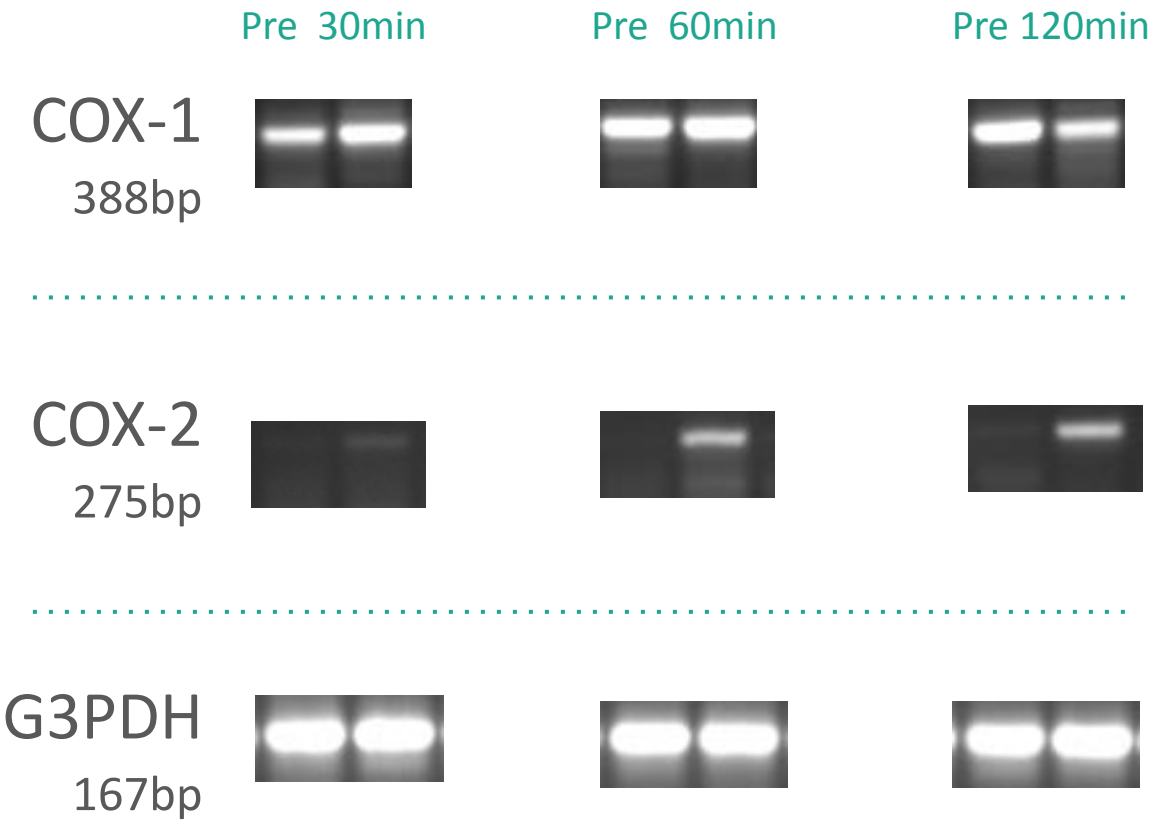
Preoperative Biopsy Site



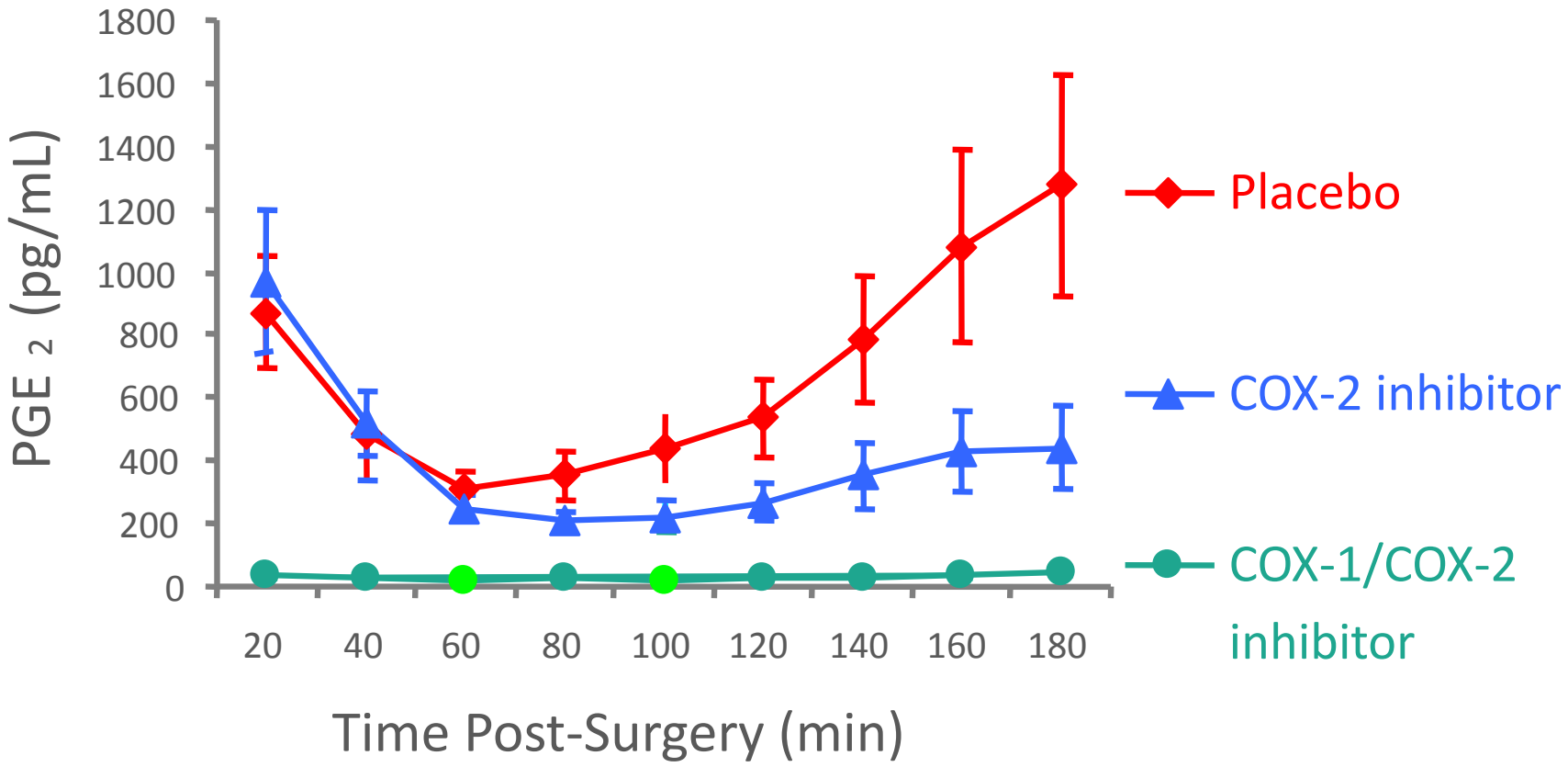
Postoperative Biopsy Site



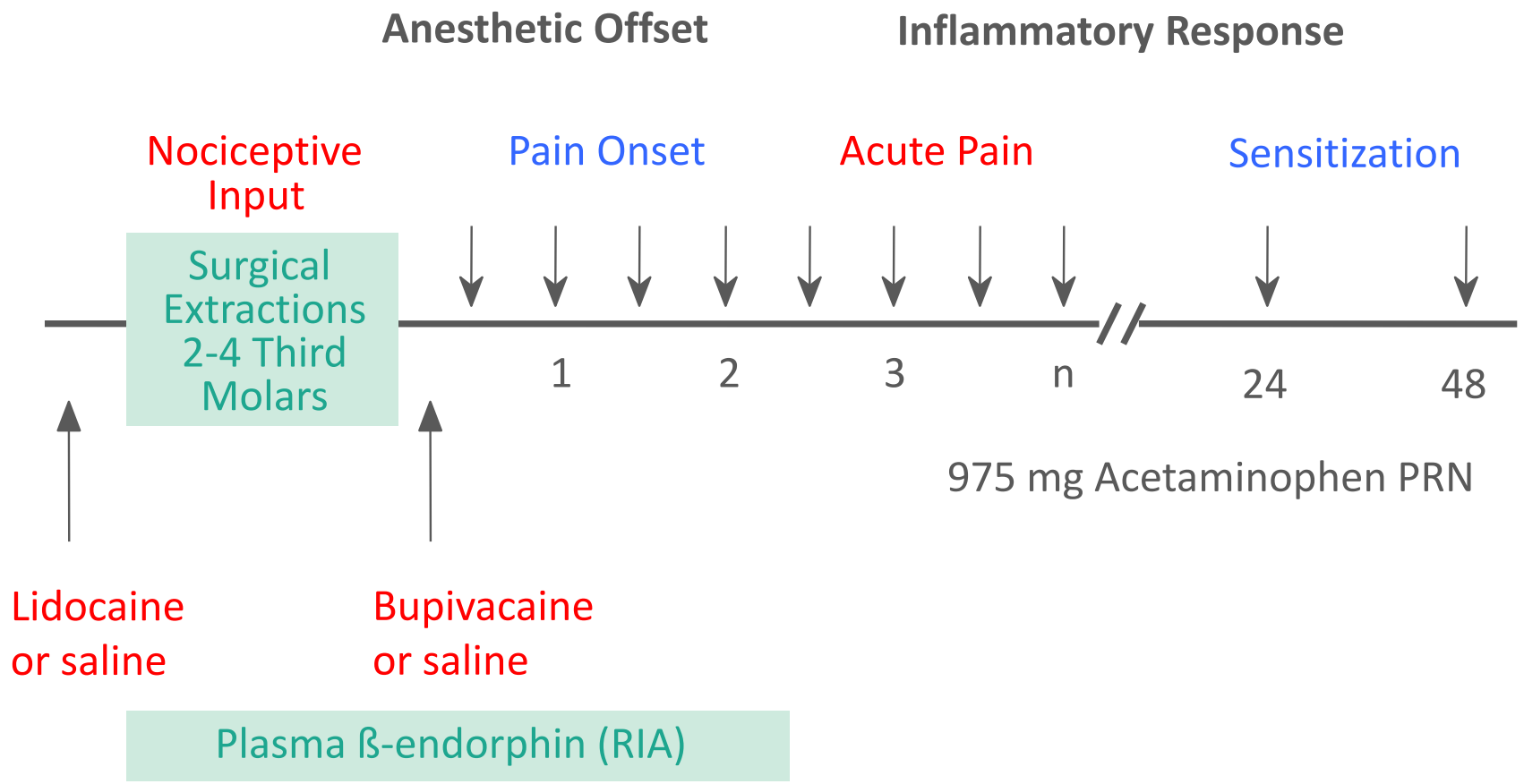


Khan 2002

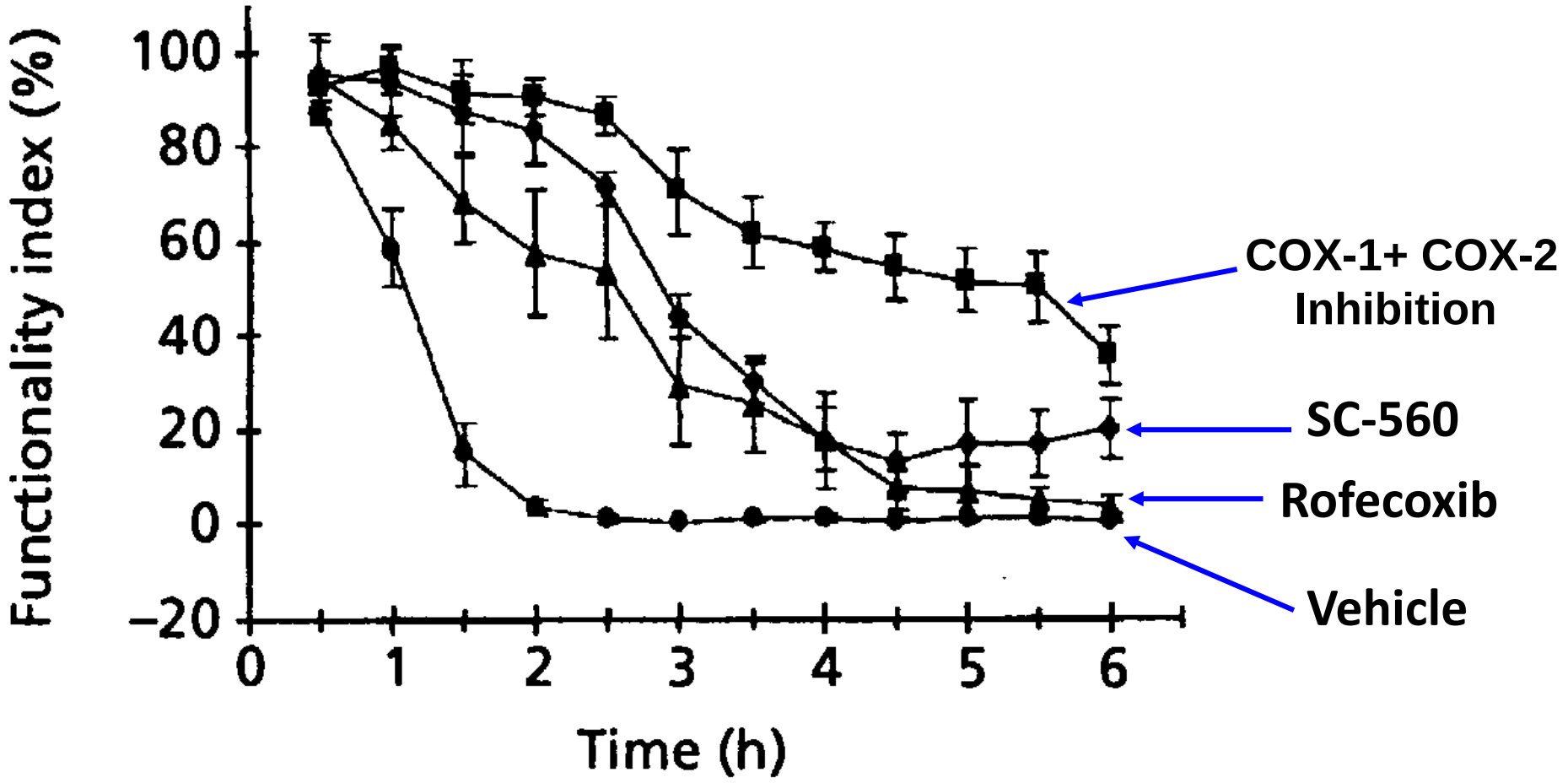
Differential Time Course of COX-1 and COX-2 Products



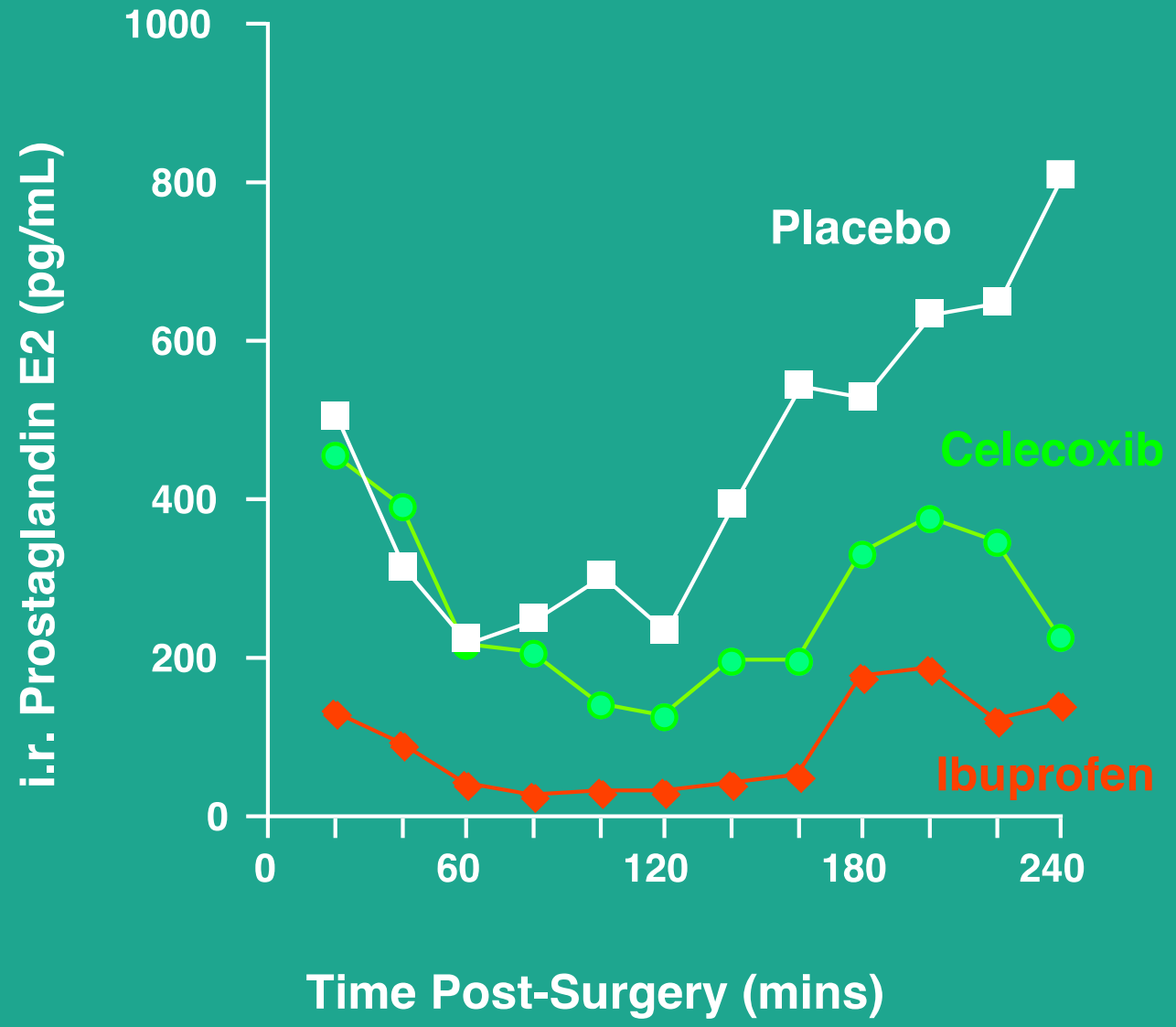
Central Sensitization: Due to Postoperative Pain Input



Contribution of COX-1 and COX-2 to Acute Inflammation



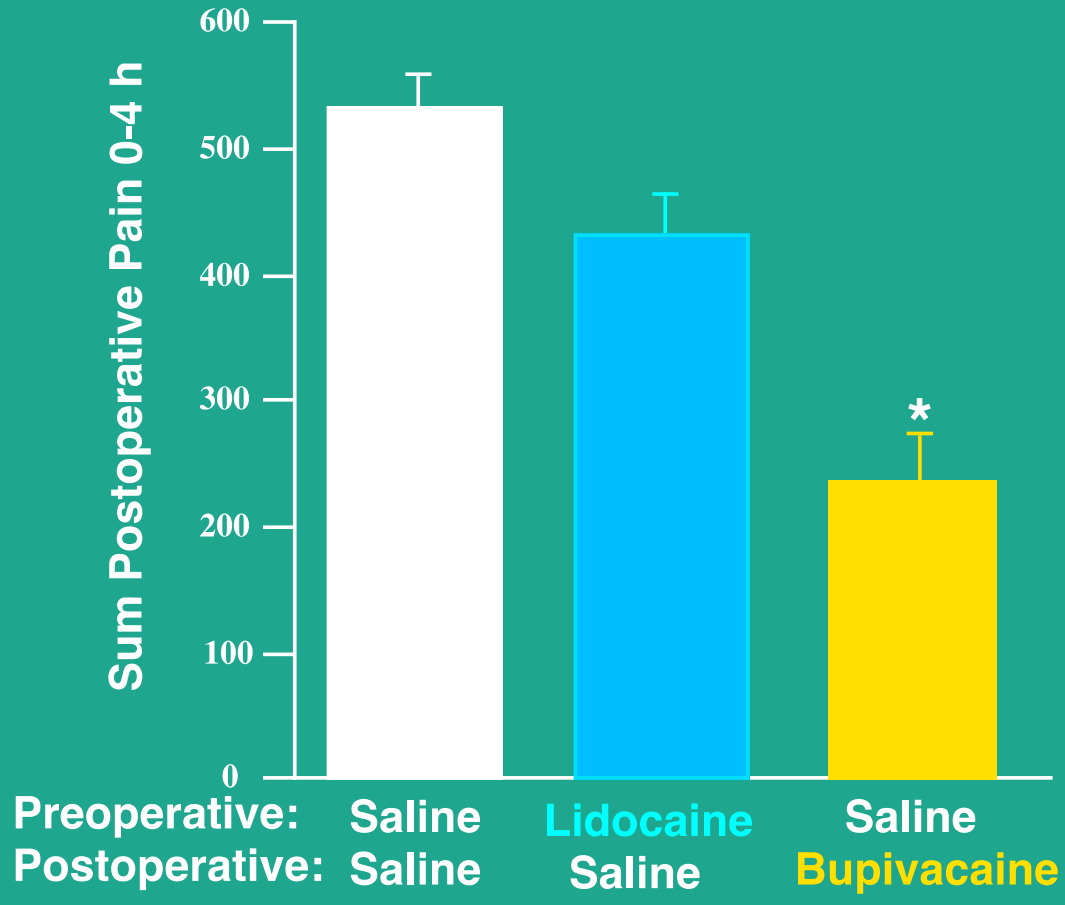
NSAID Suppression of COX-2



Khan 2002

Preventive Effects of Postop Pain Control

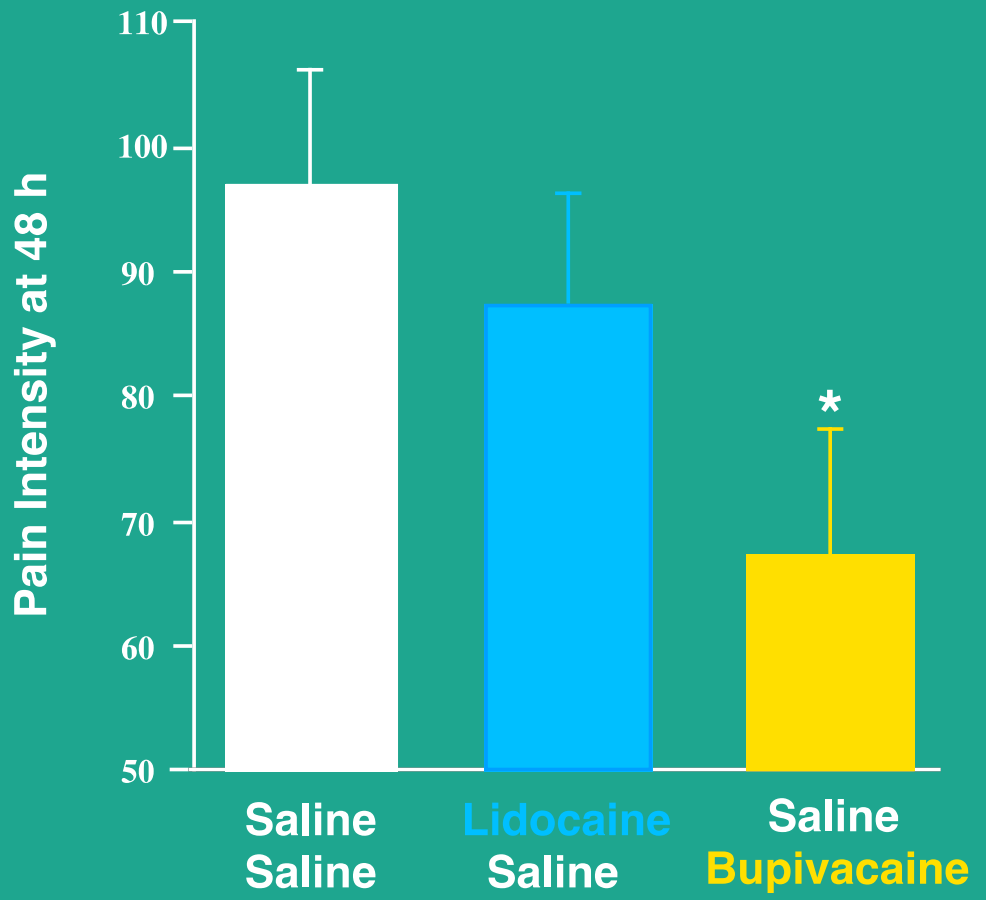
Immediate Postop. Pain



* P < 0.001 Bupivacaine drug effect, 2-ANOVA

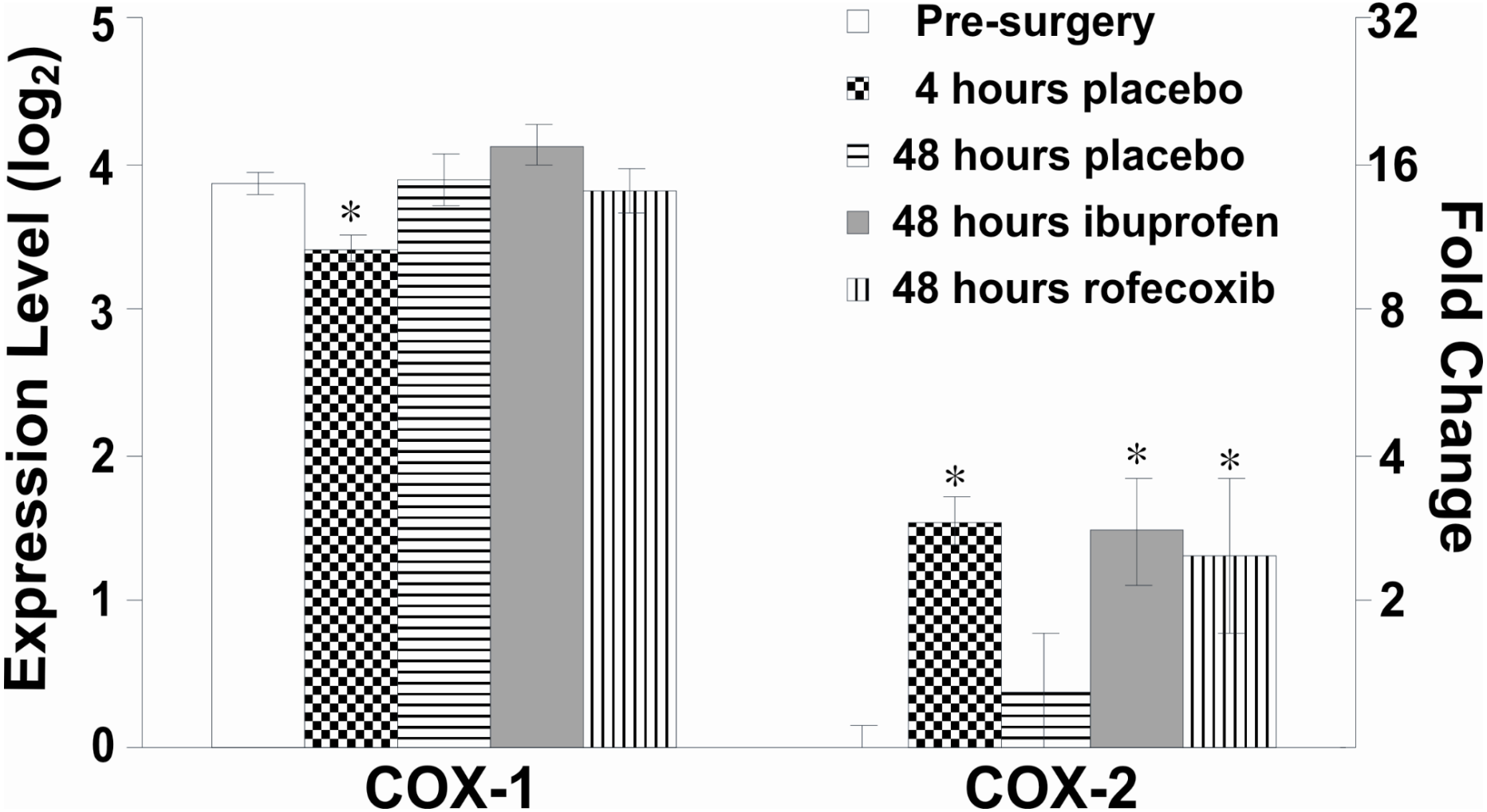
Gordon 2002

Pain at 48 Hours

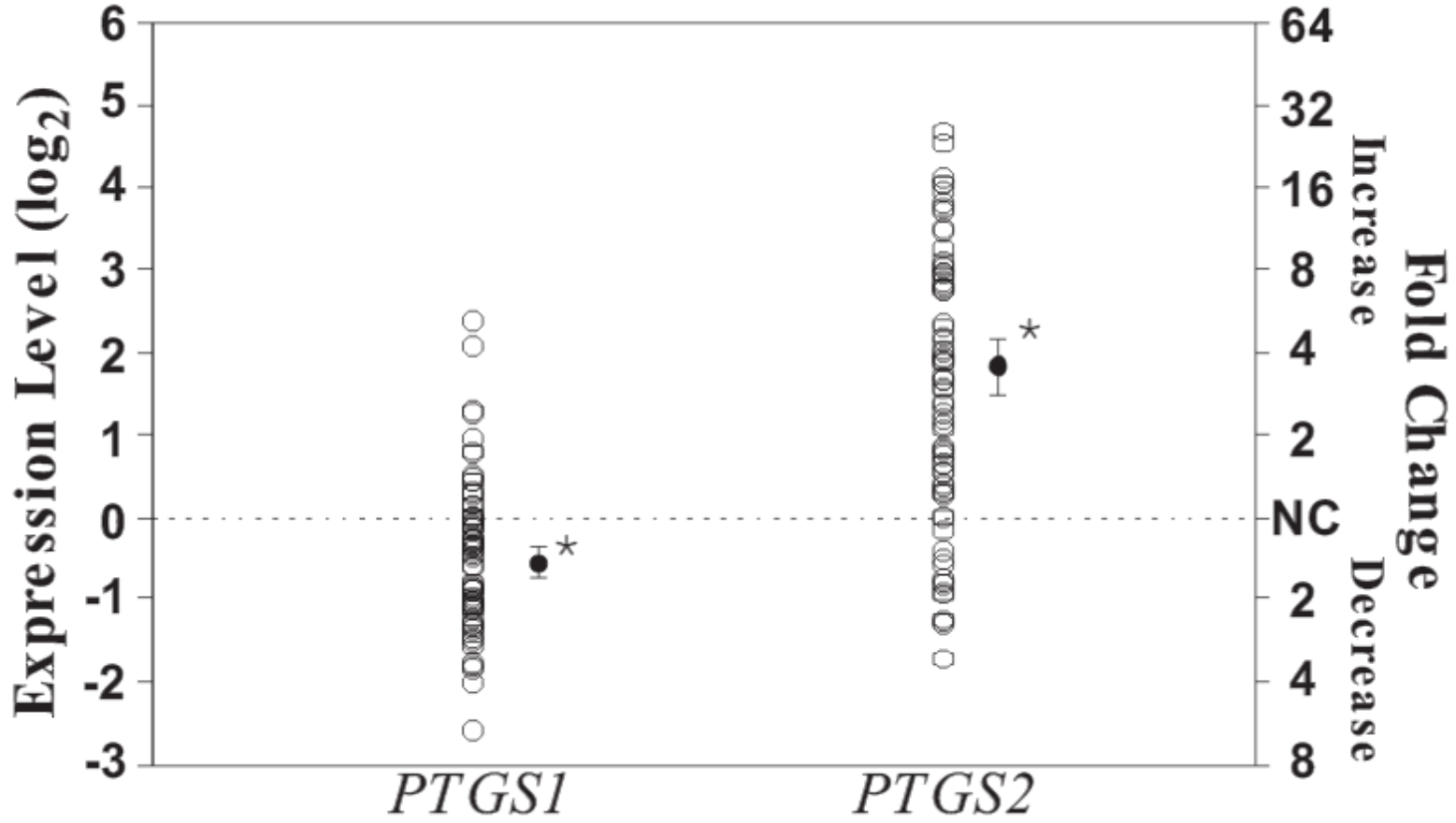


* P < 0.05 Bupivacaine drug effect, 2-ANOVA

COX-1 vs. COX-2 as Analgesic Targets



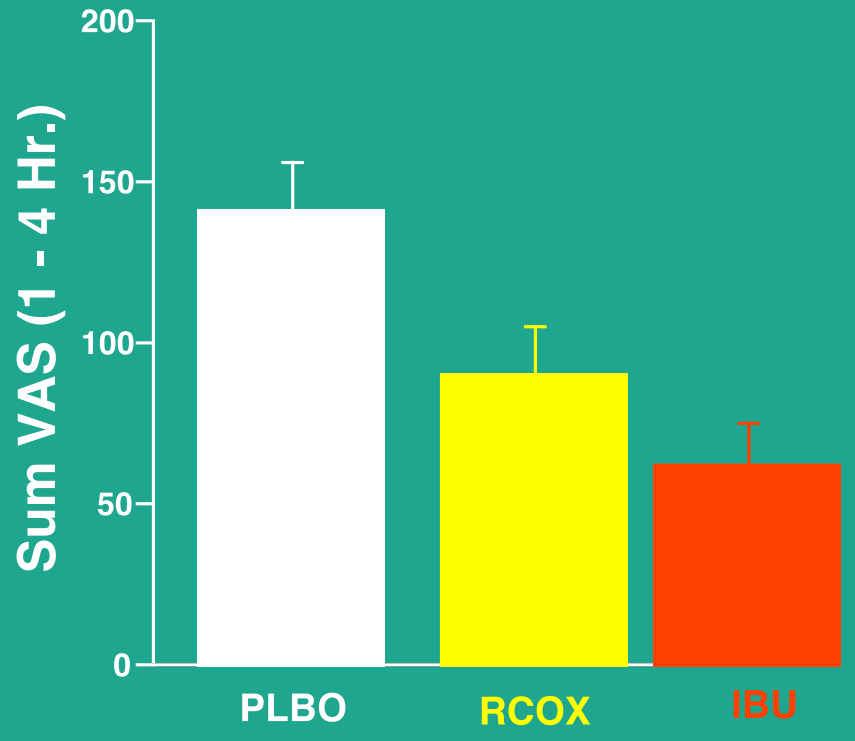
Changes in inflammatory gene expression acutely



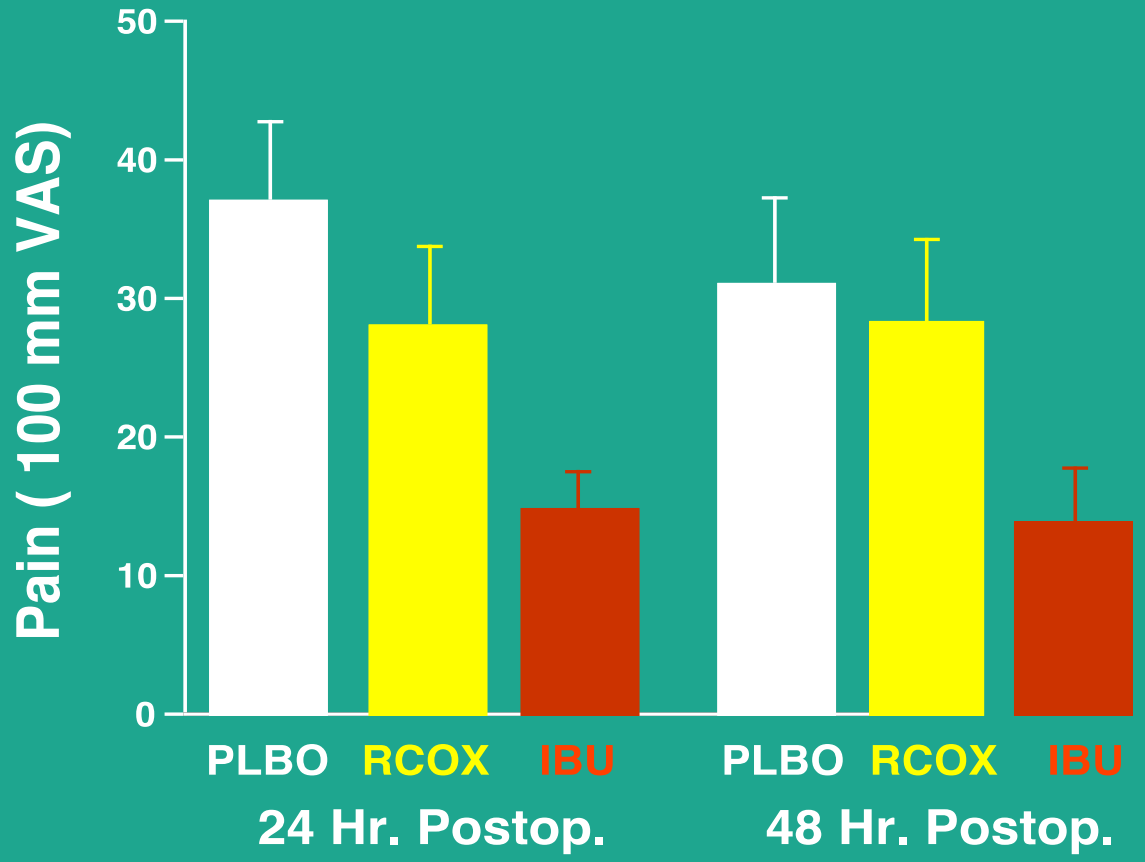
Lee 2006

Dual COX-1/COX-2 Suppression Prevents Central Sensitization

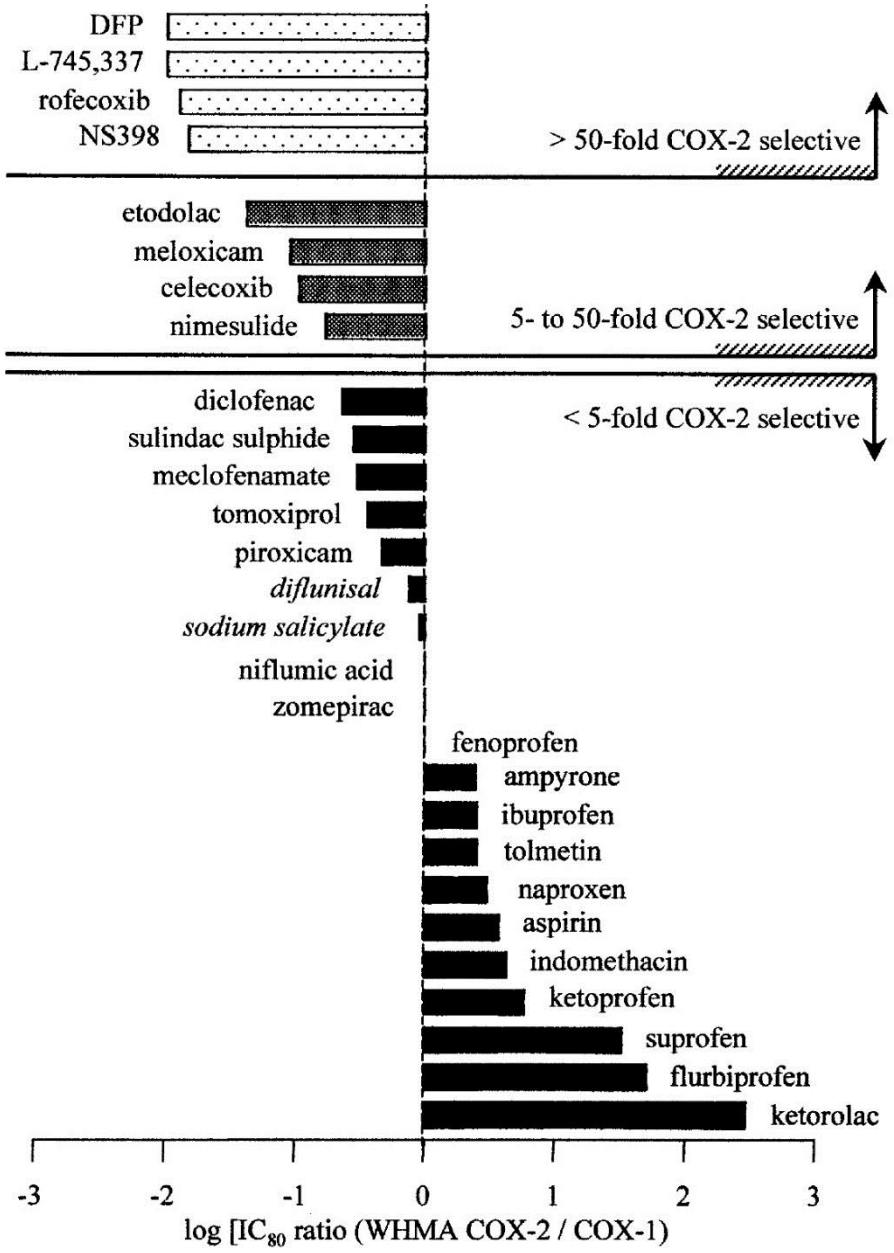
Pain Postoperatively



Pain at 24 and 48 hr



Toxicity of NSAIDs are based on their Selectivity for COX1 or COX2



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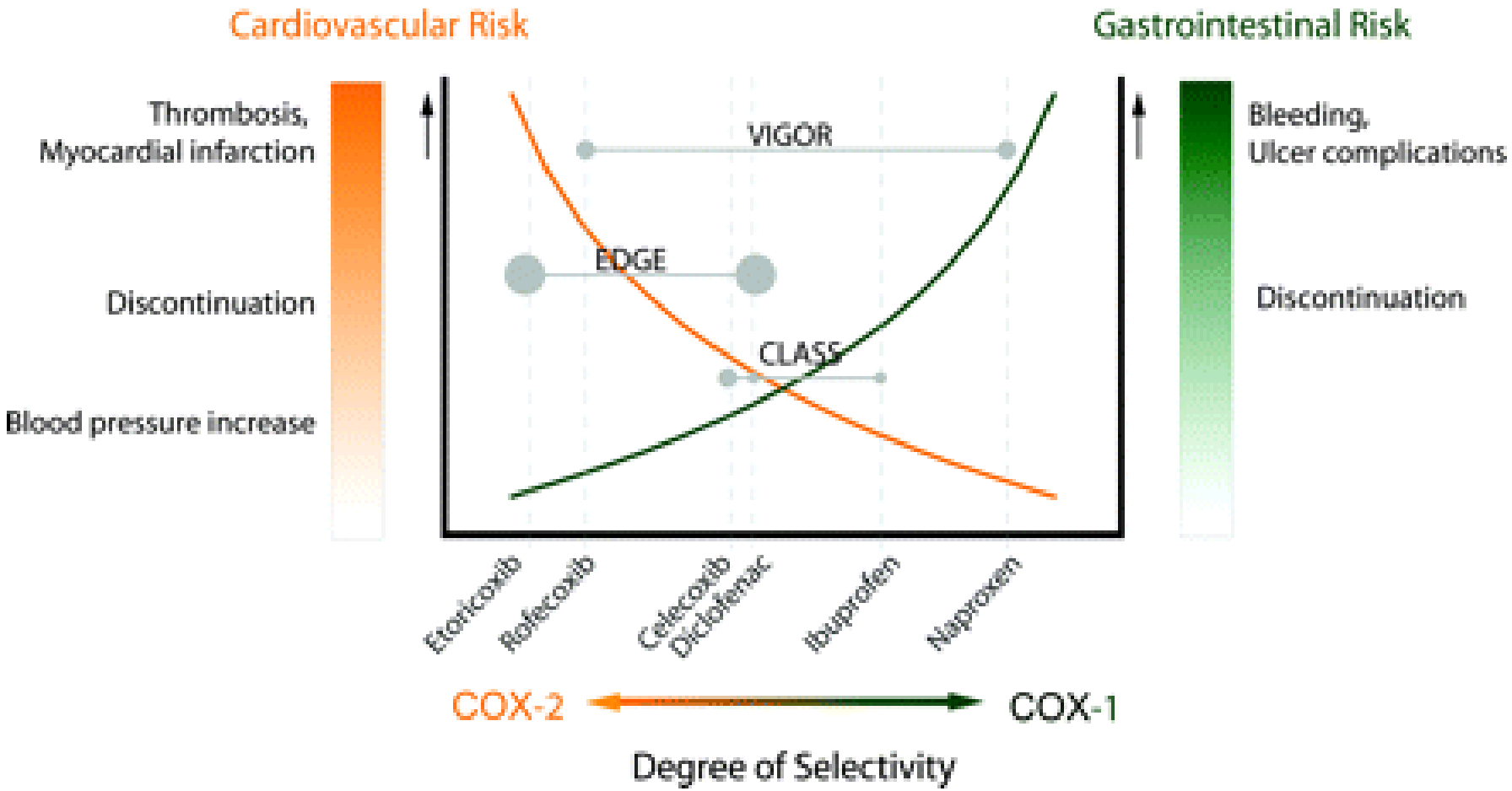
Adverse effects
GI/Cardiovascular Toxicity



Acetaminophen Mechanism of Action

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- 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?

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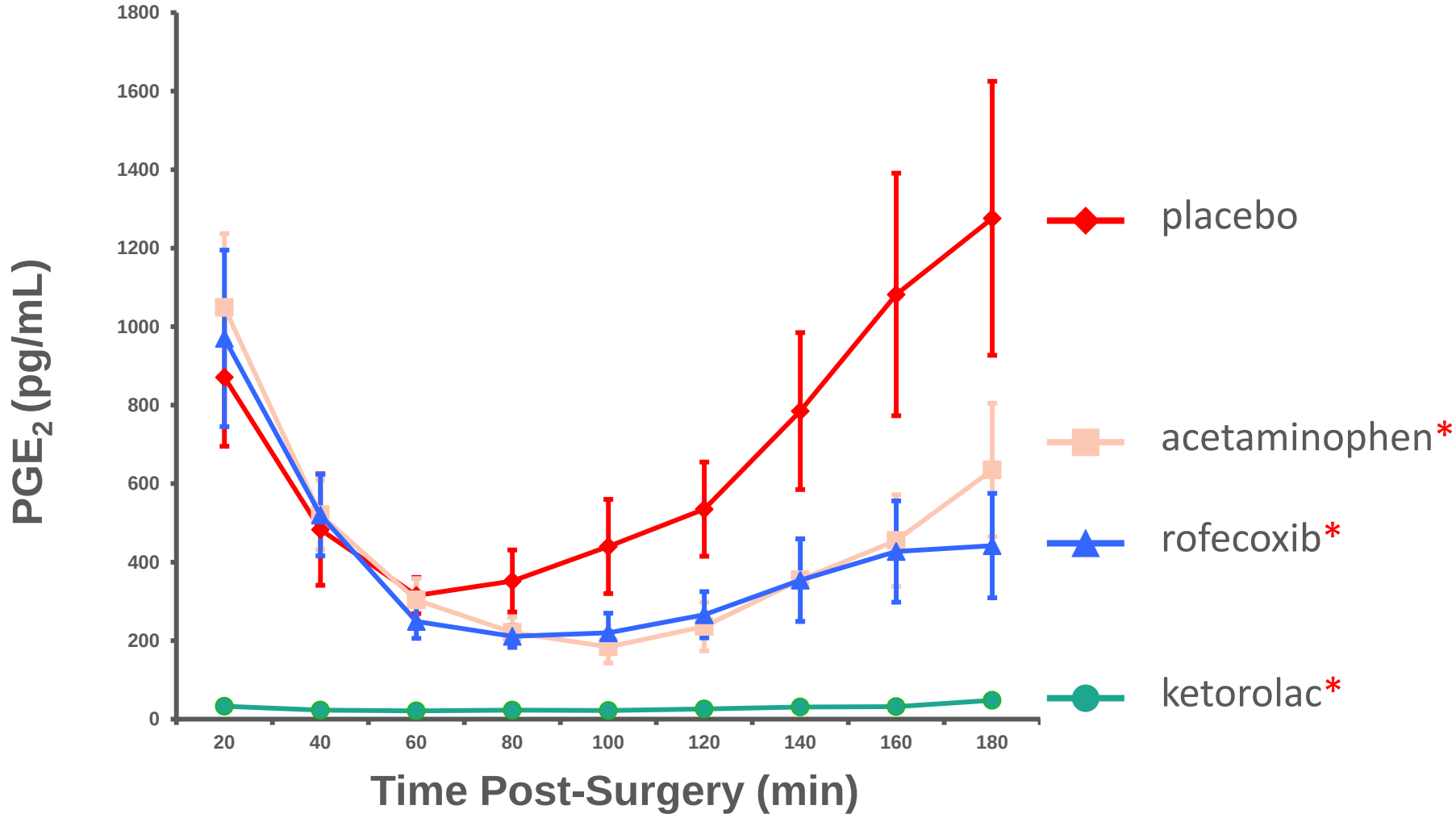
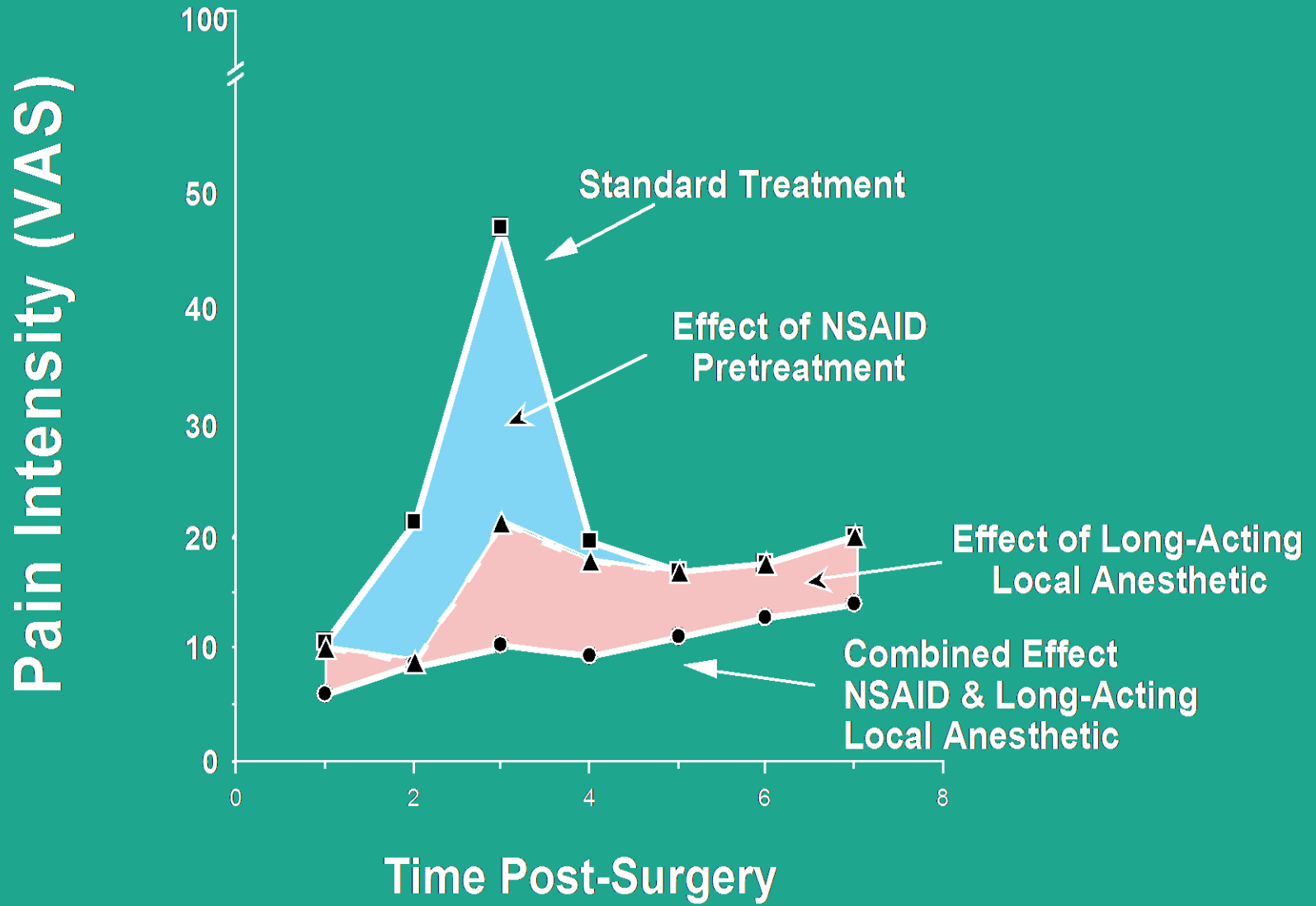


Strategies for Preventive Analgesia: Reduce Nociceptive Barrage with an NSAID and a Long-Acting Local Anesthetic



Dionne 1984

PAIN Management Paradigm

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- **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

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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

Dionne, Gordon, Moore: Compendium 2016; 37:372-378

Moderately Severe Pain

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- 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

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Relative Effects of Treatment	Opioid Combinations	Preventive/Additive/Adaptive Approach
Analgesia	++	+++
Adverse Effects	+++	+
Abuse Potential	+++	none (without opioid) + (with tramadol) ++ (with oxycodone or hydrocodone)
Overdose Risk	++	none (without opioid) + (with tramadol) ++ (with oxycodone or hydrocodone)

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

Dionne, Gordon, Moore: Compendium 2016; 37:372-378

Table 18–8

Summary of Drug Target and Site of Action of Common Drug Classes and Relative Efficacy by Pain State

DRUG CLASS (REPRESENTATIVE AGENTS IN PARENTHESES)	DRUG ACTION	SITE OF ACTION[a]	RELATIVE EFFICACY IN PAIN STATES[b]
NSAIDs (ibuprofen, aspirin acetominophen)	Nonspecific COX inhibitors	Peripheral and spinal	Tissue injury >> acute stimuli = nerve injury = 0 (Hamza and Dionne, 2009, Svensson and Yaksh, 2002)
COX 2 inhibitor (celecoxib)	COX2-selective inhibitor	Peripheral and spinal	Tissue injury >> acute stimuli = nerve injury = 0 (Hamza and Dionne, 2009)
Opioids (morphine)	μ receptor agonist	Supraspinal and spinal	Tissue injury = acute stimuli ≥ nerve injury > 0 (see this chapter)
Anticonvulsants (gabapentin)	Na^+ channel block, $\alpha_2\delta$ subunit of Ca^{2+} channel	Supraspinal and spinal	Nerve injury > tissue injury = acute stimuli = 0 (Lai et al., 2004; Taylor, 2009)
Tricyclic antidepressants (amitryptiline)	Inhibit uptake of 5-HT/NE	Supraspinal and spinal	Nerve injury ≥ tissue injury >> acute stimuli = 0 (Mochizucki, 2004)

[a]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. [b]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

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- 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.

Dionne 2016, Dionne 2015

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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?

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More resources available at the
DC Center for Rational Prescribing

doh.dc.gov/dcrx

DCRx Modules

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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