

# **Role of IV NSAIDs: Multimodal Management of Acute Pain**

# Role of NSAIDs: Multimodal Management of Acute Pain

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# Postoperative Pain Management Remains Poorly Controlled



**14% of patients have no postoperative pain**

**47% complain about moderate pain**

**39% report severe pain**

## **Why is this important?**

Poorly controlled pain is associated with impaired rehabilitation, delayed hospital discharge, and an increased risk of developing chronic pain.

# Inadequate Acute Pain Management Has Substantial Consequences for Patients

- Delayed ambulation<sup>1</sup>
- Shortened or missed rehabilitation sessions<sup>1</sup>
- Decreased quality of life<sup>2</sup>
- Increased cost of care<sup>3</sup>
- Potential for progression from acute to chronic pain<sup>4</sup>

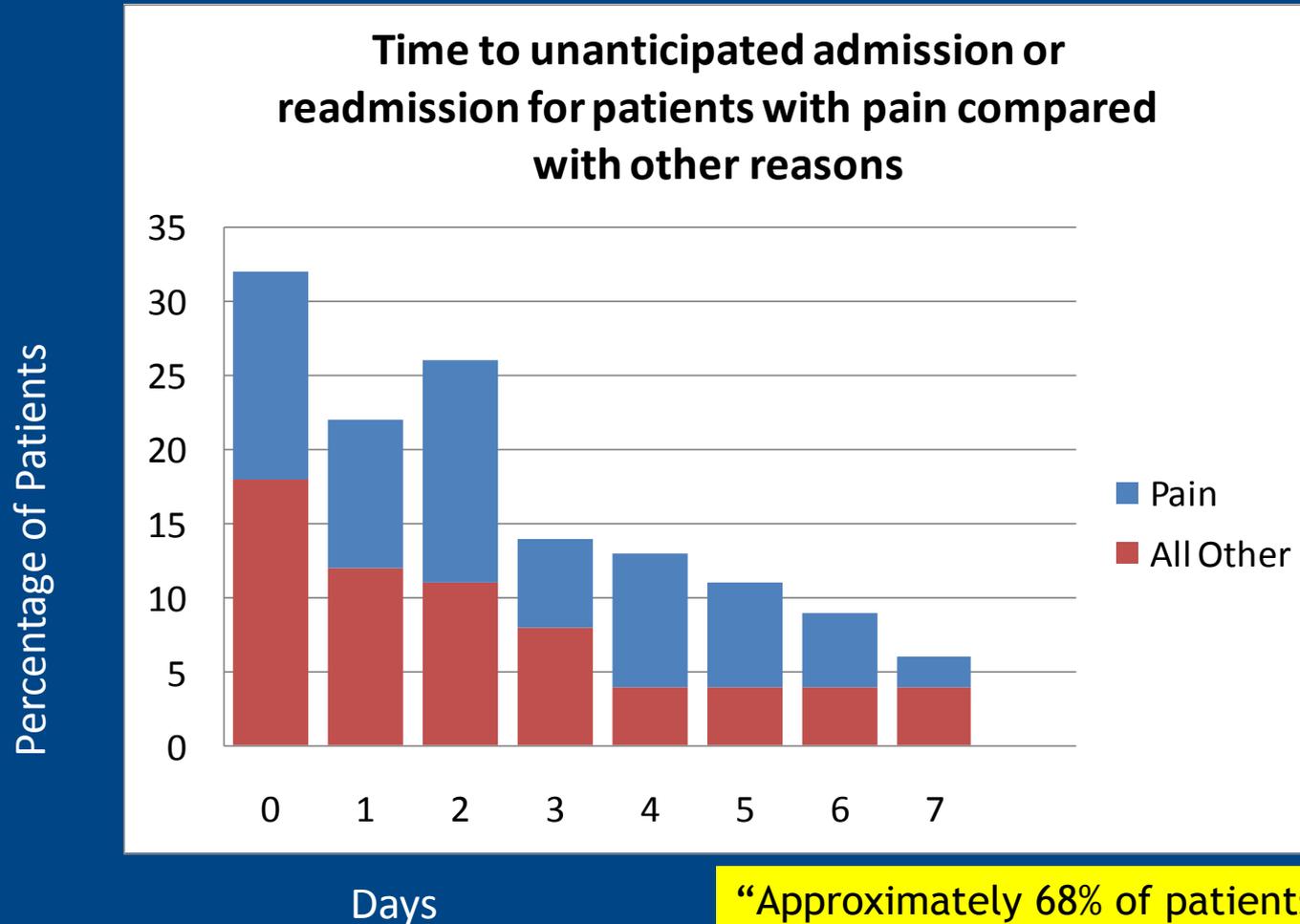
1. Morrison RS, Magaziner J, McLaughlin MA et al. *Pain*. 2003;103:303-11.

2. Wu CL, Naqibuddin M, Rowlingson AJ et al. *Anesth Analg*. 2003;97:1078-85.

3. Coley KC, Williams BA, DaPos SV et al. *J Clin Anesth*. 2002;14:349-53.

4. Pluijms WA, Steegers MAH, Verhagen AFTM et al. *Acta Anaesthesiol Scand*. 2006;50:804-8.

# UNRESOLVED PAIN LEADS TO READMISSION



“Approximately 68% of patients with pain returned to the hospital within 7 days”

# Consequences of Inadequate Acute Pain Management: Increased Cost of Care

## Mean Cost of Follow-up Care for Pain After Ambulatory Surgery

Parameter	N	Mean Cost Per Patient (USD)*
All Pain Admissions/Readmissions†	117	\$1,869
Emergency Department Visits	109	\$986
Inpatient Admissions/Readmissions	8	\$13,902

\*ased on cost of care in 1999.

† Includes ED visits

# Chronic Postoperative Pain and Disability

Procedure	Estimated incidence of chronic pain	Estimated incidence of chronic severe (disabling) pain <sup>a</sup>	Number of surgeries in the United States <sup>b</sup>
Amputation	30-50%	5-10%	159,000
Coronary artery bypass surgery	30-50%	5-10%	598,000
Thoracotomy	30-40%	10%	Unknown
Breast surgery (lumpectomy or mastectomy)	20-30%	5-10%	479,000
Cesarean section	10%	4%	220,000
Inguinal hernia repair	10%	2-4%	609,000

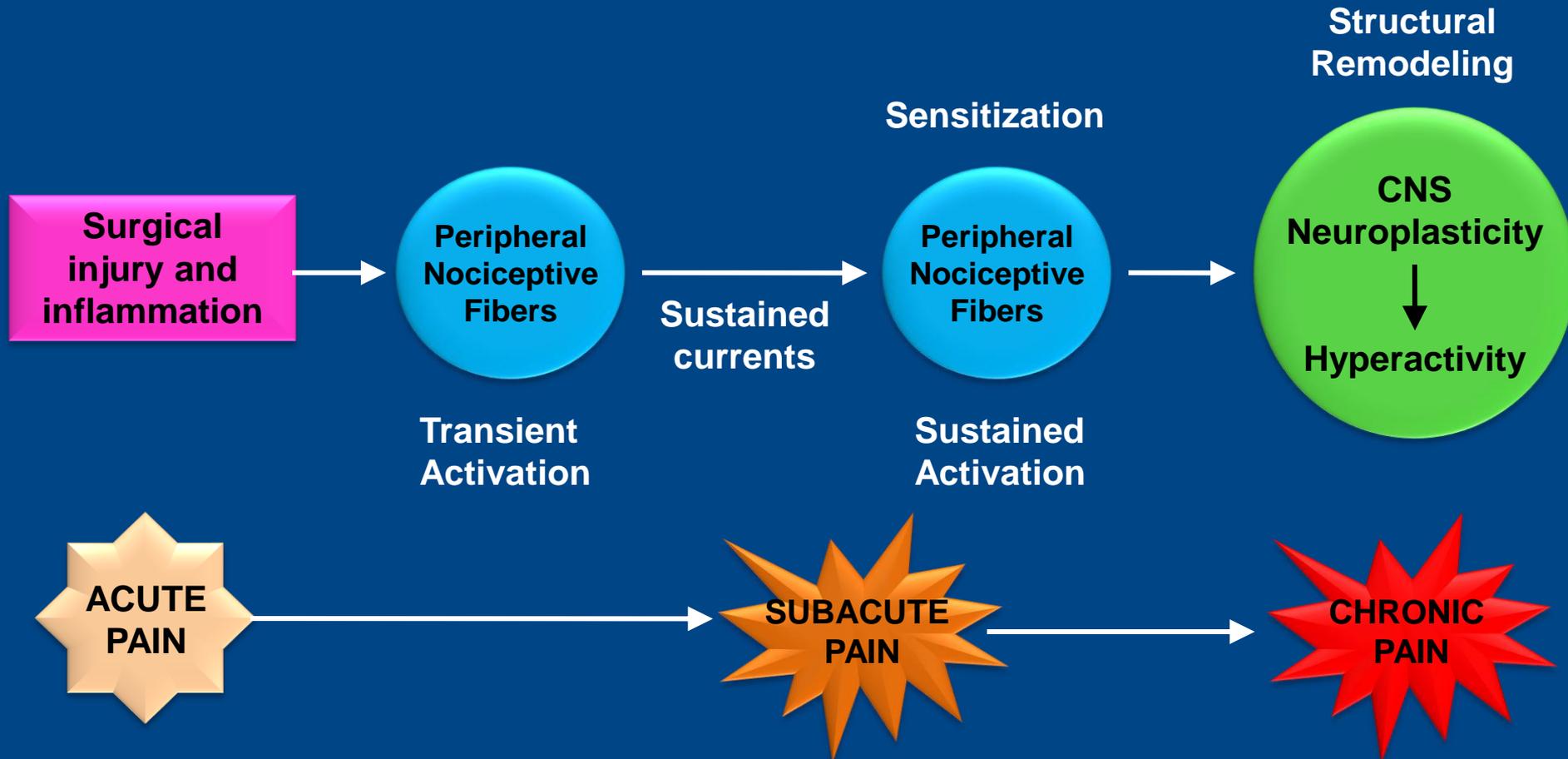
<sup>a</sup> > 5 out of 10 pain scores.

<sup>b</sup> National Center for Health Statistics, United States of America, 1996.

1.Perkins FM and Kehlet H. *Anesthesiology*. 2000;93:1123-33.

2.Kehlet H et al. *Lancet*. 2006;367:1618-25.

# Severe Acute Pain: Potential Progression to Chronic Pain



1. Woolf CJ. *Ann Intern Med.* 2004;140:441.
2. Petersen-Felix S and Curatolo M. *Swiss Med Weekly.* 2002;132:273-8.
3. Woolf CJ. *Nature.*1983;306:686-8.
4. Woolf CJ et al. *Nature.* 1992;355:75-8.

## Question:

# Why have we not improved acute pain management?

- **Lack of “pain service” or dedicated caregiver coverage**
- **Analgesic gaps**
  - Pain in PACU, following hospital discharge
- **Technology failures**
  - IV infiltration, pump mis-programming, catheter dislodgement
- **Opioid “Monotherapy”**
  - Over-reliance on IV and oral opioids
- **Opioid dependency**
  - Not recognizing opioid tolerance and adjusting therapy

1. Apfelbaum JL, Chen C, Mehta SS et al. *Anesth Analg*, 2003;97:534-40.

2. Warfield CA and Kahn CH. *Anesthesiology*.1995;83:1090-4.

# Opioid Analgesic Monotherapy Following Ambulatory Surgery

Pain Level		Treatment
Severe Pain		Even More Opioids
Moderate Pain		More Opioids
Mild Pain		Opioids

# Opioids: The Cornerstone of Pain Control

1. Powerful analgesia<sup>1</sup>
2. Multiple agents
3. Multiple delivery systems
4. High safety profile  
(cardiac, hepatorenal)

## But adverse events are common<sup>2</sup>

1. Nausea/vomiting
2. Pruritus
3. Urinary retention
4. Ileus
5. Sedation
6. Respiratory depression
7. Endocrine effects
8. Tolerance development
9. Diversion/abuse  
(rare in acute pain)

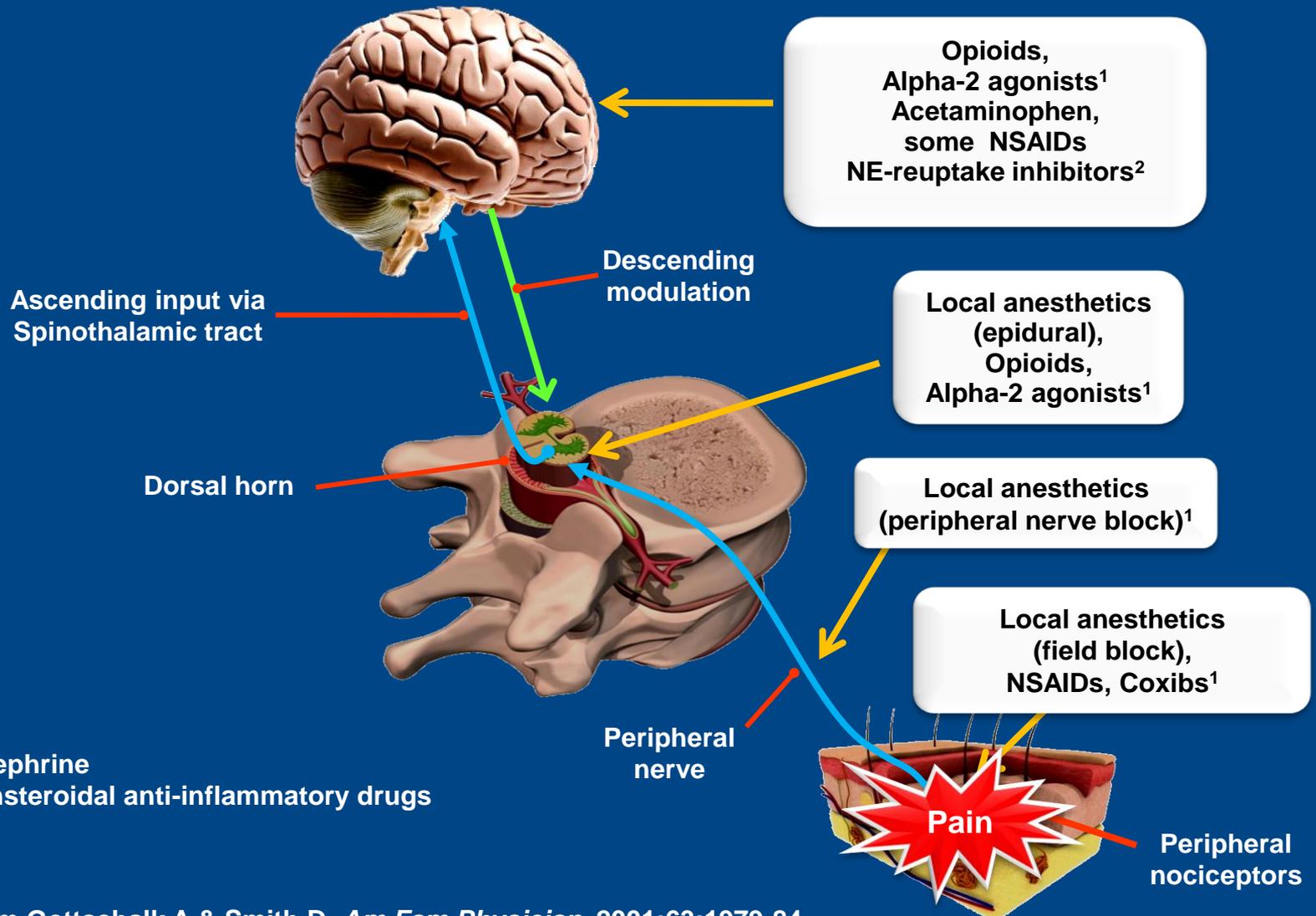
<sup>1</sup> Gutstein HB, Akil H., Opioid analgesics. In hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10<sup>th</sup> ed. New York: McGraw-Hill, 2002, pp.569 -619

<sup>2</sup> Pasero C, Portenoy RK, McCaffery M. Opioid analgesics. In McCaffery M, Pasero C, eds. Pain Clinical Manual. St. Louis, MO: Mosby, 1999, pp. 161-200.

# Multimodal (Targeted) Analgesia

**“Analgesic regimens that employ a variety of agents in small doses to block pain perception at different sites in the peripheral and central nervous system”**

# A Multimodal Approach Addresses the Complex Nature of Pain Transmission



NE = norepinephrine  
NSAIDs = nonsteroidal anti-inflammatory drugs

1. Adapted from Gottschalk A & Smith D. *Am Fam Physician*. 2001;63:1979-84.
2. Iyengar S et al. *J Pharmacol Exp Ther*. 2004;311:576-84.

# Multimodal Analgesia: Whenever Possible!

But may not be appropriate for every patient.

## Advantages

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1. Reduction in pain intensity
2. Reduction in opioid dose (opioid-sparing effect)
3. Reduction in opioid side effects
4. Improvement in surgical outcome?

## Disadvantages

1. Requires knowledge of drugs, PK data, and pharmacodynamics
2. Every analgesic has its own unique adverse event profile
3. May increase drug-drug interactions
4. Requires skills in regional and neuraxial analgesia

# Caldolor® (ibuprofen) Injection

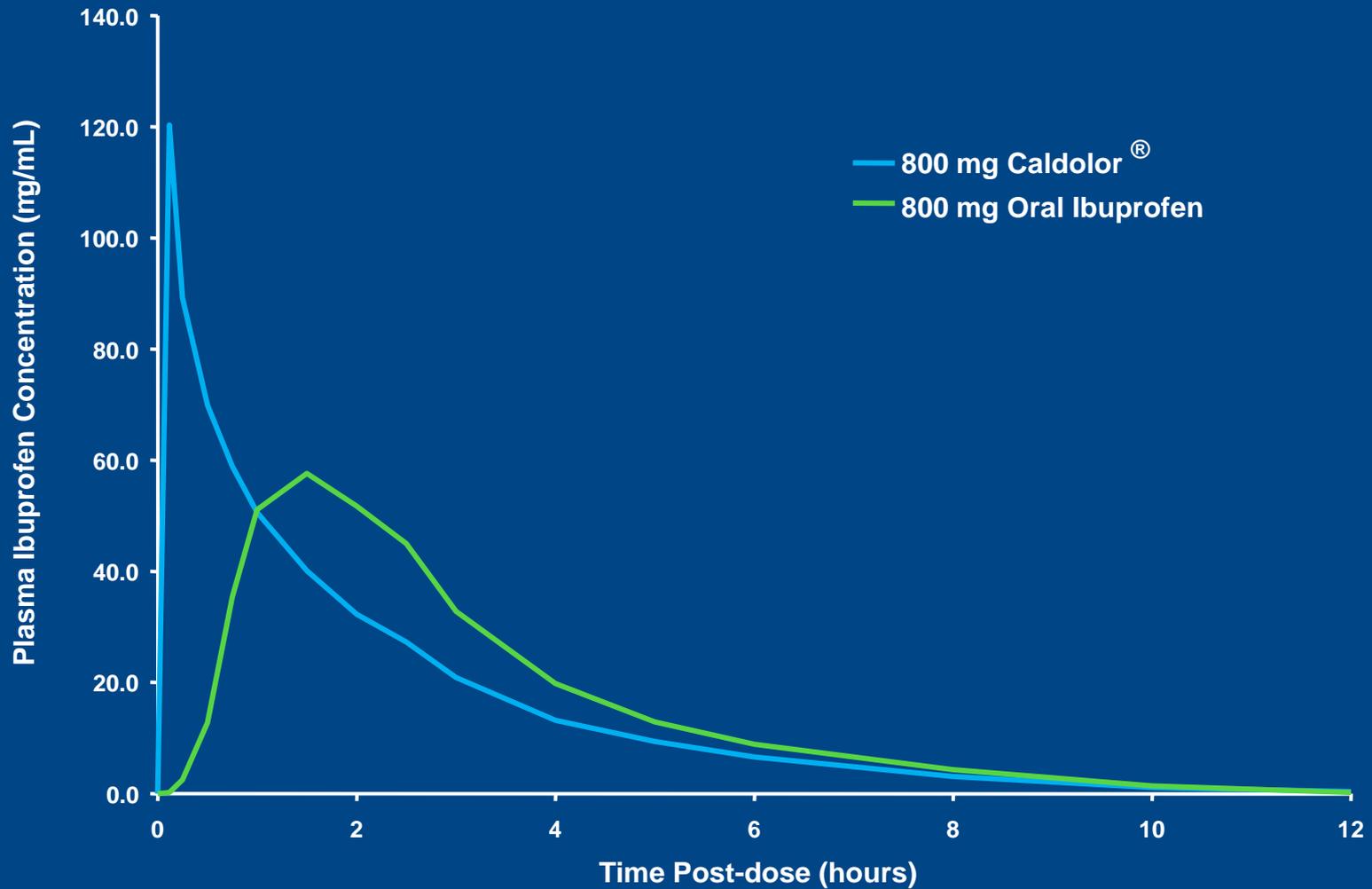
- An injectable NSAID for acute pain management. Doses of 400 and 800 mg provide reduction in post-surgical pain intensity and opioid-sparing effects.
- Indications and usage in adults
  - Management of mild to moderate pain
  - Management of moderate to severe pain as an adjunct to opioid analgesics
  - Reduction of fever
- No limitation on duration of use

**Caldolor® must be diluted prior to intravenous infusion and should NOT be given as an IV bolus or IM injection.**

# Caldolor<sup>®</sup> Clinical Development

- **PK and safety studies**
- **Fever Indication**
  - **Single-cause fever study**
  - **All-cause fever study**
- **Pain Indication**
  - **Dose ranging pain study**
  - **Abdominal hysterectomy pain study**
  - **Orthopedic pain study**

# Caldolor<sup>®</sup> PK 5-7 Minute Infusion



# Caldolor<sup>®</sup> Clinical Use

- **Indications and usage in adults:**
  - **Management of mild to moderate pain**
  - **Management of moderate to severe pain as an adjunct to opioid analgesics**
    - **Dosage\*: 400–800 mg q 6 hours as necessary for pain**
  - **Reduction of fever**
    - **Dosage\*: 400 mg followed by either 400 mg every 4-6 hours as necessary or 100-200 mg every 4 hours**
  - **Do not exceed a 3200 mg total daily dose**

# Dose-Ranging Pain Study

- Multicenter, double-blind, randomized, placebo-controlled, dose-ranging trial
- 406 adult patients undergoing elective, single-site abdominal or orthopedic surgery who received post-operative morphine\* were randomized to:

400 mg Caldolor®	N = 138
800 mg Caldolor®	N = 134
Placebo	N = 134

- Caldolor® and placebo were initiated intra-operatively and administered q 6 hours for 8 doses and then as needed q 6 hours for up to 5 days following surgery

\*Morphine by patient-controlled analgesia or patient request.

# Results of Dose-Ranging Pain Study

- **Pain at rest vs. narcotic alone over 24 hours**
  - 7% median reduction with 400 mg ( $P = 0.057$ )
  - 20% median reduction with 800 mg ( $P = 0.001$ )
  - At hour 24, 33% median reduction with 800 mg ( $P = 0.009$ )
- **Pain with movement vs. narcotic alone over 24 hours**
  - 9% median reduction with 400 mg ( $P = 0.021$ )
  - 14% median reduction with 800 mg ( $P = 0.002$ )
  - At hour 24, 18% median reduction with 800 mg ( $P = 0.005$ )

Parameter	400 mg	800 mg
Reduction in median narcotic use	3%	22%
Reduction in mean narcotic use*	5%	10%

\* $P=NS$ . In this dose-ranging, phase 3, multicenter, randomized, double-blind, placebo-controlled trial (N=406), adult postoperative abdominal or orthopedic surgery patients received 400 mg or 800 mg of Caldolor or placebo for up to 5 days.

# Abdominal Hysterectomy Pain Study

- Multicenter, double-blind, placebo-controlled trial of 319 women who had undergone elective abdominal hysterectomy
- In addition to morphine by PCA pump or patient request, patients were randomized to receive:

**800 mg Caldolor<sup>®</sup>**

**N = 166**

**Placebo**

**N = 153**

- Caldolor<sup>®</sup> and placebo were initiated intra-operatively and administered q 6 hours for 8 doses and then as needed q 6 hours for up to 5 days following surgery

PCA = Patient-controlled analgesia.

# Results of Abdominal Hysterectomy Pain Study

- **Pain at rest vs. narcotic alone over 24 hours**
  - 21% median reduction with 800 mg ( $P = 0.011$ )
- **Pain with movement vs. narcotic alone over 24 hours**
  - 14% median reduction with 800 mg ( $P = 0.010$ )

Parameter	800 mg
Reduction in median narcotic use	19%
Reduction in mean narcotic use	16% ( $P < 0.001$ )

- In this Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (N = 319), adult postoperative abdominal hysterectomy surgery patients received 800 mg of Caldolor<sup>®</sup> or placebo for up to 5 days.

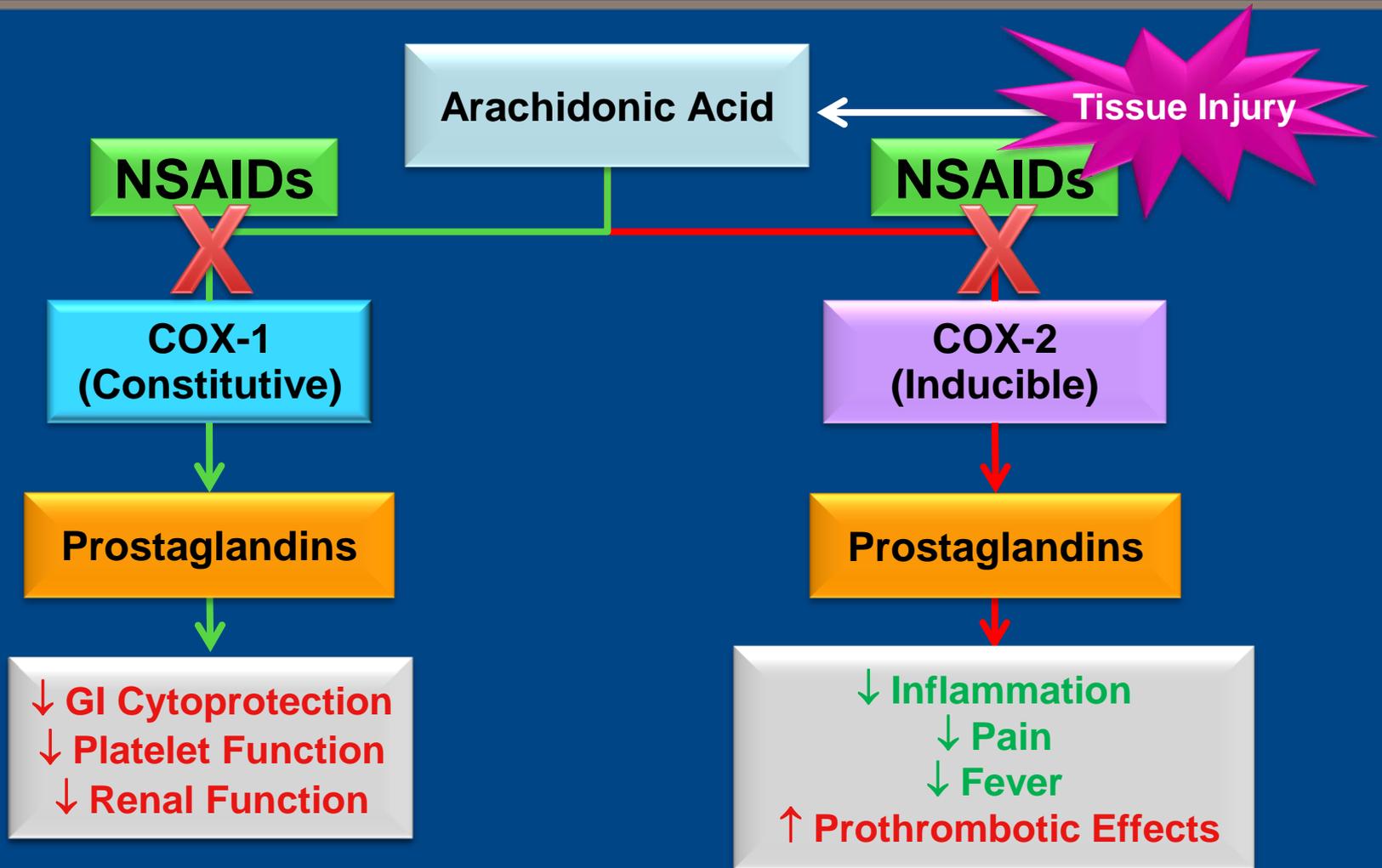
# Adverse Events in Pain Studies

Event	Caldolor®		Placebo (N = 287)
	400 mg (N = 134)	800 mg (N = 304)	
<b><i>Any Reaction</i></b>	<b>118 (88%)</b>	<b>260 (86%)</b>	<b>258 (90%)</b>
<b>Nausea</b>	<b>77 (57%)</b>	<b>161 (53%)</b>	<b>179 (62%)</b>
<b>Vomiting</b>	<b>30 (22%)</b>	<b>46 (15%)</b>	<b>50 (17%)</b>
<b>Flatulence</b>	<b>10 (7%)</b>	<b>49 (16%)</b>	<b>44 (15%)</b>
<b>Headache</b>	<b>12 (9%)</b>	<b>35 (12%)</b>	<b>31 (11%)</b>
<b>Hemorrhage</b>	<b>13 (10%)</b>	<b>13 (4%)</b>	<b>16 (6%)</b>
<b>Dizziness</b>	<b>8 (6%)</b>	<b>13 (4%)</b>	<b>5 (2%)</b>
<b>Edema peripheral</b>	<b>1 (&lt;1%)</b>	<b>9 (3%)</b>	<b>4 (1%)</b>
<b>Urinary retention</b>	<b>7 (5%)</b>	<b>10 (3%)</b>	<b>10 (3%)</b>
<b>Anemia</b>	<b>5 (4%)</b>	<b>7 (2%)</b>	<b>6 (2%)</b>
<b>Decreased hemoglobin</b>	<b>4 (3%)</b>	<b>6 (2%)</b>	<b>3 (1%)</b>
<b>Dyspepsia</b>	<b>6 (4%)</b>	<b>4 (1%)</b>	<b>2 (&lt;1%)</b>
<b>Wound hemorrhage</b>	<b>4 (3%)</b>	<b>4 (1%)</b>	<b>4 (1%)</b>
<b>Abdominal discomfort</b>	<b>4 (3%)</b>	<b>2 (&lt;1%)</b>	<b>0</b>
<b>Cough</b>	<b>4 (3%)</b>	<b>2 (&lt;1%)</b>	<b>1 (&lt;1%)</b>
<b>Hypokalemia</b>	<b>5 (4%)</b>	<b>3 (&lt;1%)</b>	<b>8 (3%)</b>

# Summary

- **Poorly controlled pain is associated with impaired rehabilitation, delayed hospital discharge, and an increased risk of developing chronic pain.**
- **Optimal pain relief may require a multimodal approach thus achieving analgesia at multiple points along the pathway.**
- **IV NSAIDs can be used in the multimodal management of postoperative acute pain.**

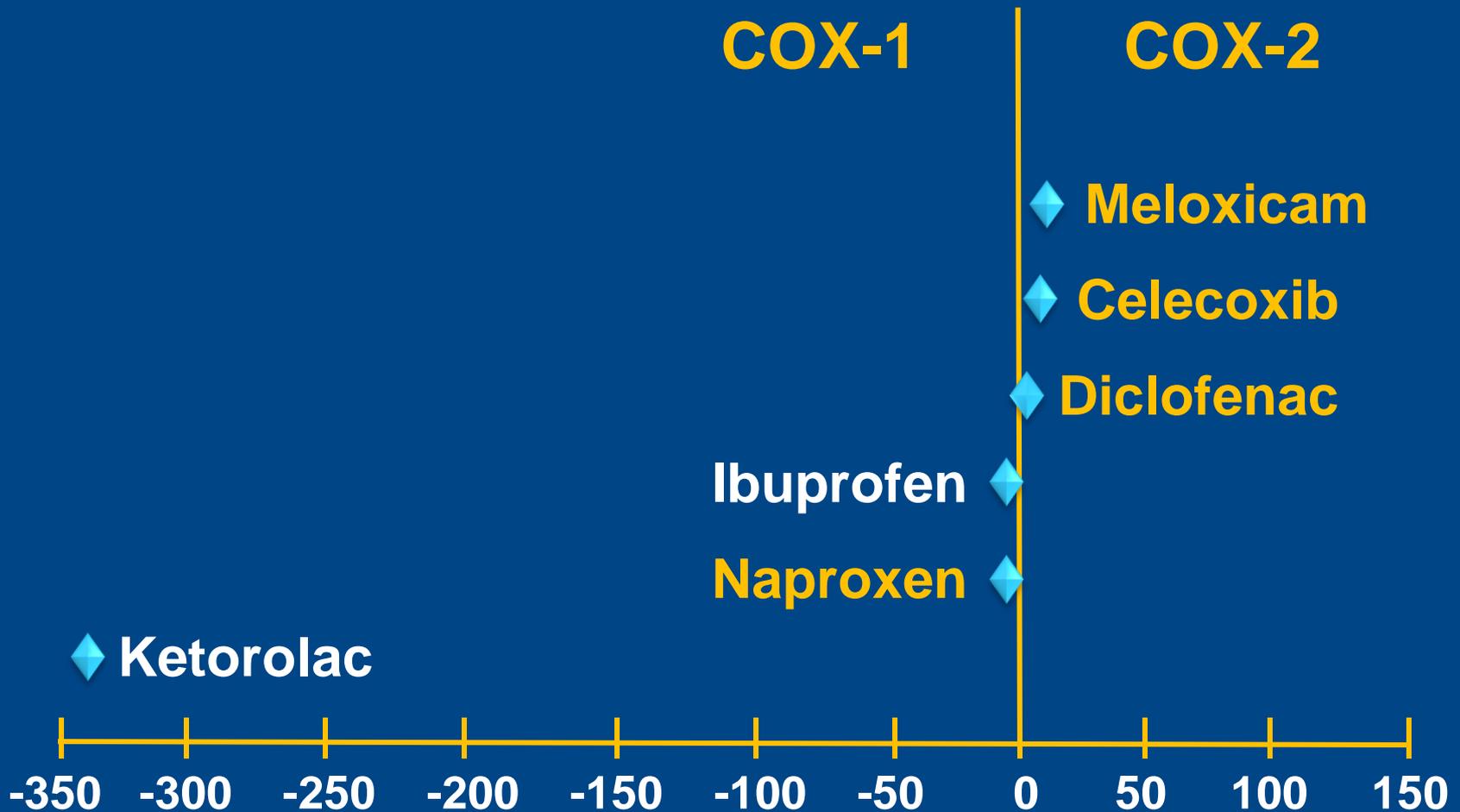
# NSAIDs Mechanism of Action



COX = cyclooxygenase; GI = gastrointestinal

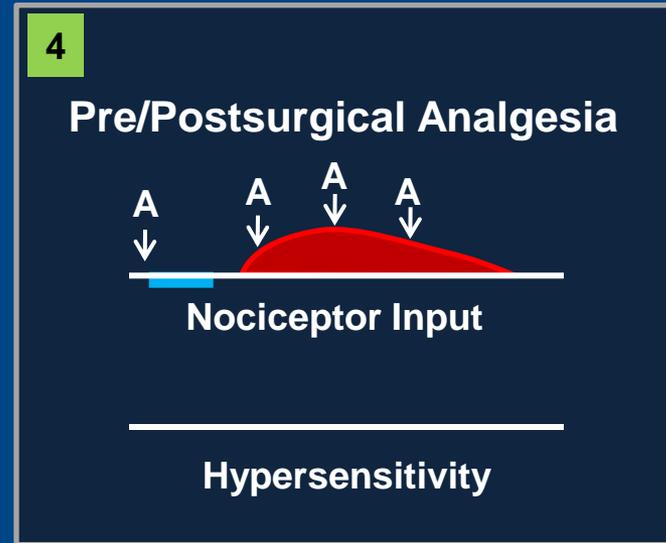
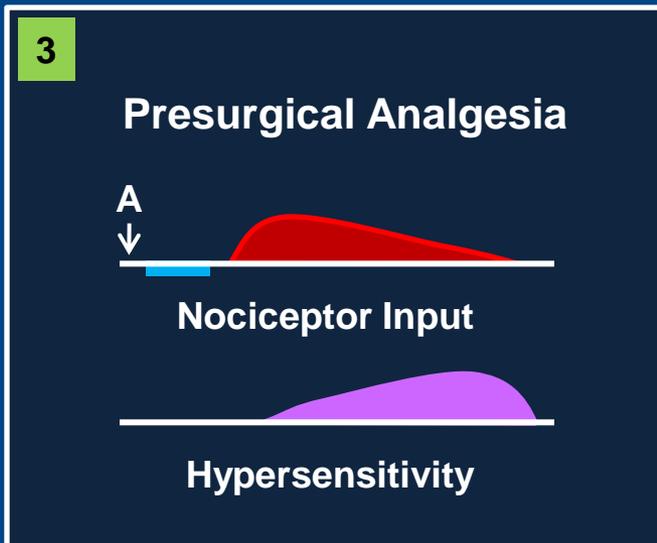
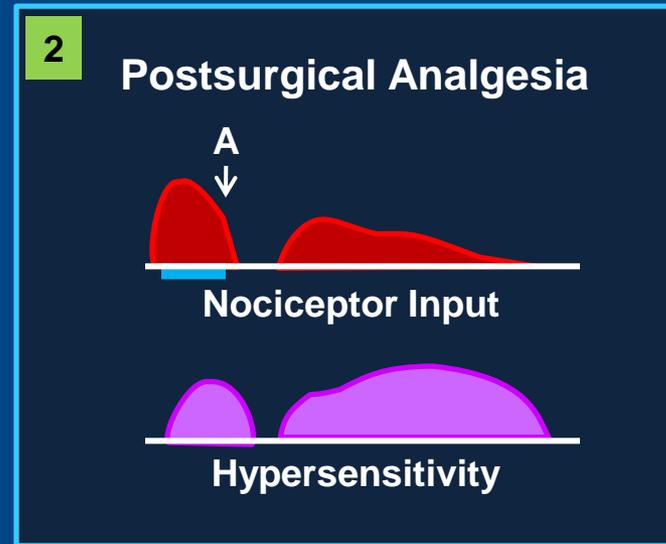
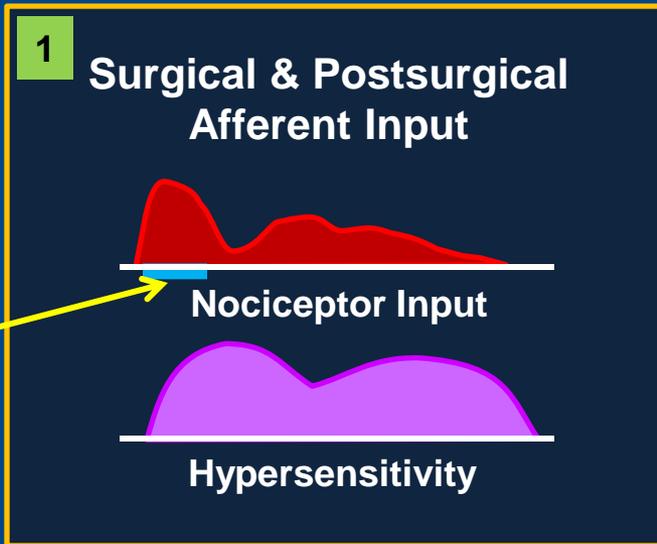
Adapted from Solomon GD. Nonopioid and adjuvant analgesics. In: Tollison CD, Satterthwaite JR, Tollison JW, eds. *Practical Pain Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:243–52.

# Inhibition of COX-2 Relative to COX-1



# Preemptive Analgesia May Reduce Wound Hypersensitivity

Intensity  
Duration of Surgery  
Duration



# Caldolor<sup>®</sup> (ibuprofen) Injection

**Caldolor<sup>®</sup> must be diluted prior to intravenous infusion and should NOT be given as an IV bolus or IM injection.**

- **Indications and usage in adults**
  - Management of mild to moderate pain
  - Management of moderate to severe pain as an adjunct to opioid analgesics
  - Reduction of fever
- **Clinical data support preoperative dosing**
- **No limitation on duration of use**

# Orthopedic Pain Study

- **Multicenter, double-blind, placebo-controlled trial**
  - 185 patients
  - Elective orthopedic surgery
    - Knee or hip replacement, reconstruction, or arthroplasty
- In addition to morphine by PCA pump or patient request, patients were randomized to receive:

**800 mg Caldolor<sup>®</sup>**

**N = 99**

**Placebo**

**N = 86**

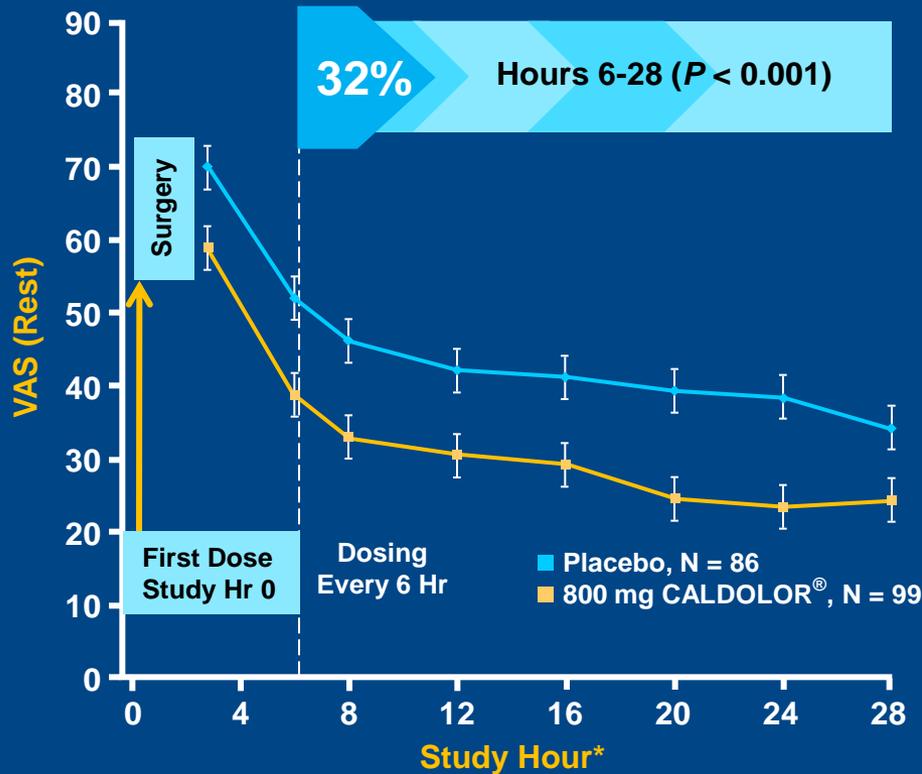
- **Caldolor<sup>®</sup> and placebo were initiated at induction and administered q 6 hours for 5 doses and then as needed q 6 hours for up to 5 days following surgery**

PCA = patient-controlled analgesia

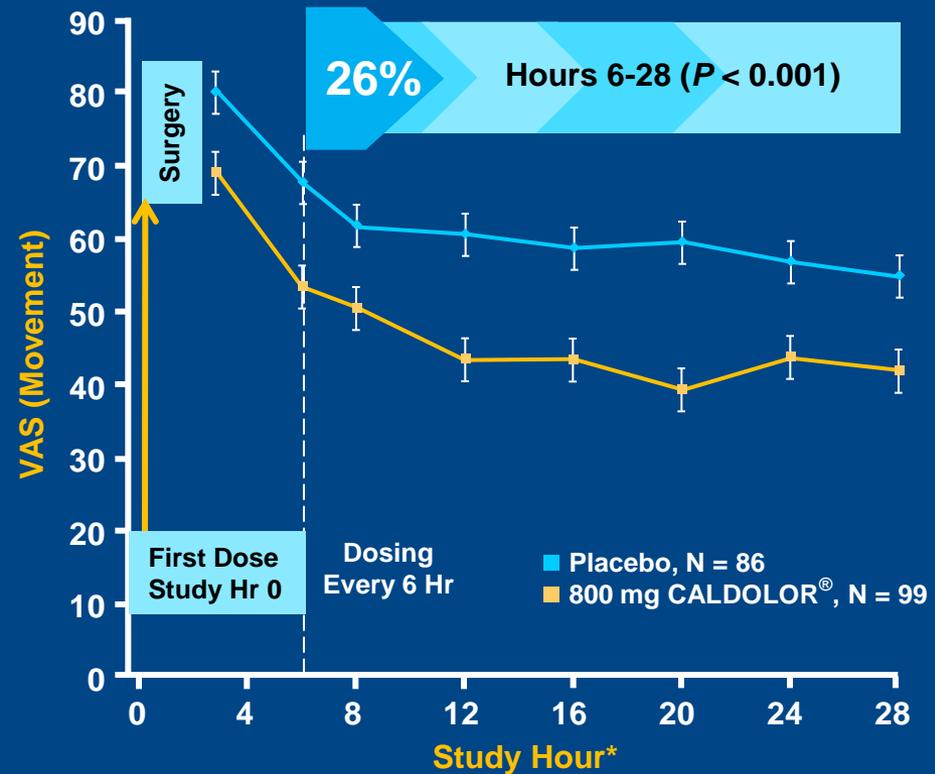
# Orthopedic Pain Study: VAS Scores at Rest and With Movement

## Reduction in Pain Intensity Scores After Orthopedic Surgery

Assessed at Rest



Assessed With Movement



VAS = visual analog scale

\* Statistical significance was demonstrated at each assessment point.

# Morphine Dose Requirements Following Orthopedic Surgery

Placebo Group



Caldolor® (ibuprofen)  
Group



Patients treated with Caldolor  
used **31% less** morphine

# Adverse Events in Orthopedic Pain Study

<b>Number of patients experiencing at least one adverse event</b>	<b>Placebo (N = 86) 74 (86%)</b>		<b>800 mg Caldolor® (N = 99) 90 (91%)</b>	
<b>Adverse events that differed significantly between treatment groups</b>				
<b>Type of adverse event</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
<b>Vomiting</b>	<b>12</b>	<b>14%</b>	<b>27</b>	<b>27%</b>
<b>Dyspepsia</b>	<b>4</b>	<b>5%</b>	<b>0</b>	<b>0</b>

- **Incidence of transfusion and bleeding-related adverse events were no different between the Caldolor (ibuprofen) Injection and placebo groups.**

# Caldolor® (ibuprofen) Injection Warnings

- **Cardiovascular risk**

- NSAIDs may increase risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Risk may increase with duration of use.
- Caldolor is contraindicated for the treatment of perioperative pain in the setting of CABG surgery.

- **Gastrointestinal risk**

- NSAIDs increase risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.
  - Events can occur at any time without warning symptoms.
  - Elderly patients are at greater risk.

NSAID = Nonsteroidal anti-inflammatory drug; CABG = Coronary artery bypass graft; GI = Gastrointestinal

Caldolor Prescribing Information.

Full prescribing information can be accessed at [www.caldolor.com](http://www.caldolor.com).

# Caldolor<sup>®</sup> (ibuprofen) Injection Contraindications

- Patients with known hypersensitivity to ibuprofen
- Patients experiencing asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs
- Treatment of perioperative pain in the setting of coronary artery bypass graft surgery

# Summary

- **IV NSAIDs can be used in the multimodal management of postoperative acute pain.**
- **Caldolor® (ibuprofen) Injection is the only IV ibuprofen available for treatment of adults in:**
  - **Mild-to-moderate pain as a single agent**
  - **Moderate-to-severe pain as adjunct to opioid analgesics**
- **Study results suggest Caldolor increased pain relief when used preemptively and throughout the postoperative period and decreased narcotic consumption.**
- **In this clinical trial, there was no significant difference in renal, cardiac, or bleeding adverse events versus placebo.**