Adjuvant Agents in Pain Medicine

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Opioids prescribed <u>for the treatment of chronic pain</u> have been associated with "increased" risk of opioid overdose. Politicians & Payers have responded by developing opioid dose limitation policies.
Adjuvants drugs have become important.

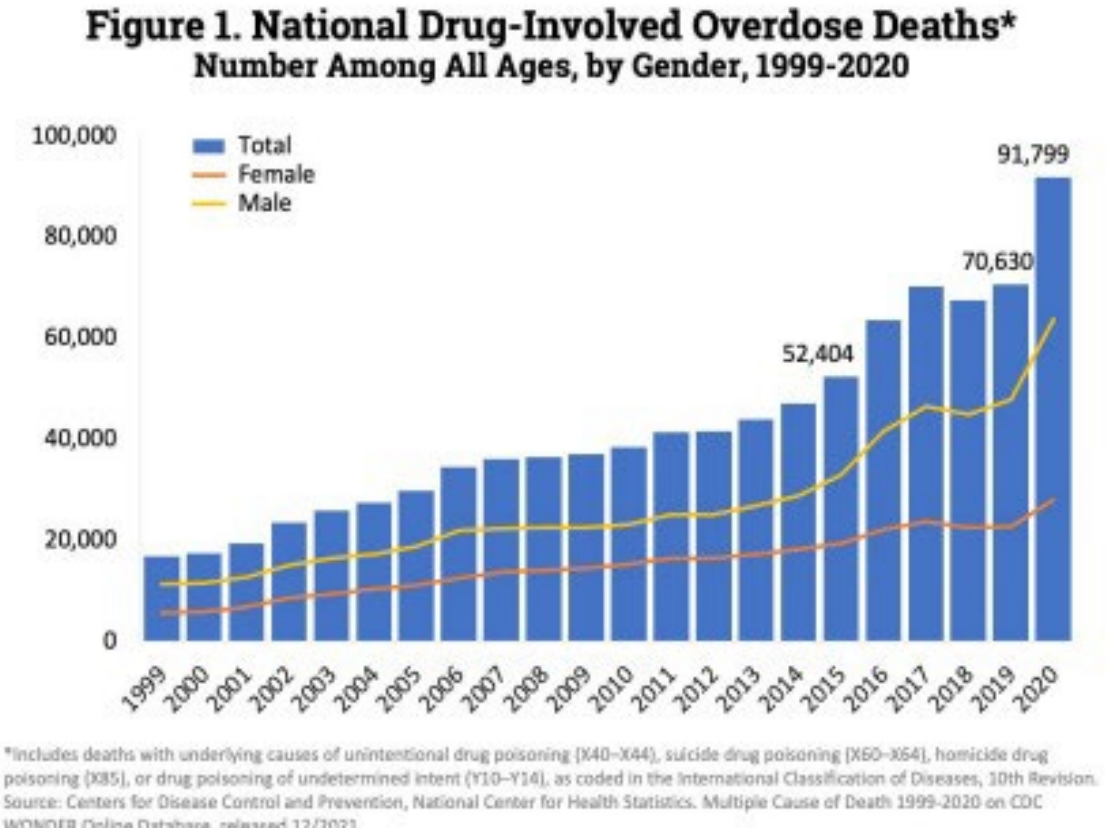
Deaths related to drug overdose->

->Life expectancy had been declining pre-pandemic-> driven mostly by drugs, alcohol and suicide driven-the use of opioids associated with a 15 year reduction in life expectancy.

- *A REVIEW OF OPTIONS- THEIR POTENTIAL ADVANTAGES & CAUTIONS WITH A FOCUS ON POTENTIAL OPIOID-SPARING BENEFITS OF ADJUVANTS-*

A report from a national overdose detection program indicates that overdoses have increased significantly in recent years.

Is Undertreated Pain Causing Patient Suicides?



Our treatment options should focus on safety, efficacy and cost effectiveness.

Are we trying to treat <u>specific complaints</u> or are we just trying to comply with government policies for reducing opioid prescription quantities & Milligram Morphine Equivalent's (MME's) ?

CONCERNS ABOUT OPIOID DOSES?

->MOVE BEYOND OPIOIDS?

GOAL: By utilizing Opioid-Sparing drugs-> allow the patient to feel a similar level of pain relief while taking fewer *opioids*

LESS EUPHORIA? LESS ABUSE POTENTIAL? LESS MISUSE?- *OPIOID-SPARING BENEFITS OF ADJUVANTS FACT OR FICTION?*

GOAL:

***Treatment Goal*: O*pioids* for CHRONIC PAIN MANAGEMENT= (*30*% improvement)**

PAIN GOALS ARE NOT ALWAYS THE SAME =
back pain, migraine, osteoarthritis, fibromyalgia, and diabetic neuropathy

VA - *Opioid* Safety Initiative (OSI)=

Goal is to take the edge off and *reduce pain* by ***20–30%***

https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/Pain_ChronicPainProviderEducationalGuide_IB101000.pdf

Canadian Guideline for Opioid Use for Pain

The physician should ensure the patient's expectations are **realistic.** The goal of opioid therapy for **chronic** non-cancer pain is rarely the elimination of pain, but rather an improvement in function or a reduction of pain intensity by at **least 30%**

http://nationalpaincentre.mcmaster.ca/opioid/cgop_b01_r05.html

Cannabis as Adjunct Medication:

Improved sleep, less nausea, less suicide, reduced anxiety & depression …*RARELY, AFTER INITIATION OF MJ TO A REGIMEN-ARE "LOWER" OPIOID DOSES ABLE TO BE UTILIZED?*

$=Patient pays 100% for THC,CBD…

- *OPIOID-SPARING BENEFITS OF ADJUVANTS ?*

Some clinical studies not only have failed to demonstrate that THC relieves pain but have also found that the drug has the opposite effect. In these experiments, volunteers who experienced painful shocks, heat, or pressure from a tourniquet reported that THC actually increase their sensitivity to pain.

HTTPS://WWW.NCBI.NLM.NIH.GOV/BOOKS/NBK224384/

EFFICACY OF CANNABIS-BASED MEDICINES FOR PAIN MANAGEMENT=

The results of 43 RCTs (a total of 2,437 patients) were included in this review, of which 24 RCTs (a total of 1,334 patients) were eligible for meta-analysis. This analysis showed limited evidence showing more pain reduction in chronic pain -0.61 (-0.78 to -0.43, P < 0.0001), especially by inhalation -0.93 (-1.51 to -0.35, P = 0.001) compared to placebo. Moreover, even though this review consisted of some RCTs that showed a clinically significant improvement with a decrease of pain scores of 2 points or more, 30% or 50% or more, the majority of the studies did not show an effect. Consequently, although the primary analysis showed that the results were favorable to CBMs over placebo, the clinical significance of these findings is uncertain.

PAIN PHYSICIAN. 2017 SEP;20(6):E755-E796. EFFICACY OF CANNABIS-BASED MEDICINES FOR PAIN MANAGEMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

J AVIRAM, G SAMUELLY-LEICHTAG

Antipyretics

ANTIPYRETICS= NSAIDS AND APAP! WHAT WE SHOULD REMEMBER

NSAIDs RX & OTC= 70 million prescriptions annually in the US.

Classified as nonselective or selective based upon their effects on the COX-1 & COX-2 enzymes.

All but one are nonselective NSAIDs =These products reversibly inhibit the COX-1 and COX-2 enzymes, resulting in a reduction in prostaglandin precursors and subsequent antipyretic, analgesic, and anti-inflammatory effects.

Celecoxib is the only "selective" NSAID currently available. This agent selectively inhibits the activity of the COX-2 enzyme, producing similar therapeutic effects as nonselective NSAIDs while potentially reducing gastrointestinal (GI) adverse events (e.g., GI bleeding)

Diclofenac
Etodolac
Fenoprofen
Flurbiprofen
Ibuprofen
Indomethacin
Ketoprofen
Ketorolac
Meclofenamate
Mefenamic acid
Meloxicam
Nabumetone
Naproxen
Oxaprozin
Piroxicam
Sulindac
Tolmetin

Combination products

Treximet is a combination medication used to treat migraines attacks= Naproxen/ sumatriptan

ARTHROTEC® (diclofenac sodium/misoprostol)

Duexis contains a combination of famotidine and ibuprofen. Famotidine is a histamine blocker. Famotidine works by decreasing the amount of acid the stomach produces. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID). Ibuprofen works by reducing hormones that cause inflammation and pain in the body.

VIMOVO (**naproxen** and **esomeprazole magnesium**) is combination of a nonsteroidal anti-inflammatory drug and a PPI available as an oval, yellow, multi-layer, delayed-release tablet combining an **enteric-coated naproxen** core and an immediate-release **esomeprazole** magnesium layer surrounding the core.

Existence of a ceiling effect to the dose response curve with NSAID administration:

This ceiling effect results in an increase in adverse effects without additional pain relief once an analgesic ceiling is reached.

Conventional nonopioid analgesics are associated with beneficial antipyretic effects and do not produce physical or psychological dependence. These agents may be discontinued suddenly without a risk of withdrawal symptoms as seen with chronic opioid administration.

ANTIPYRETICS: Acetaminophen & NSAIDs

- Historical Considerations:

  - Prostaglandins ubiquitous
  - Originally thought to originate in prostate termed “prostaglandins” from Goldblatt & Von Euler in 1930’s
  - Vane demonstrated that aspirin, indomethacin, and NSAID’s all were inhibitors of cylooxygenase in 1971.
  - Habenicht in 1985 & later work in 1990 by Needleman demonstrated an endogenous COX-1 & an inducible enzyme COX-2 existed
  - COX 2 inhibitors developed 1999

- Clinical Pearls= I always ask my pt’s- Are you stiff in the morning? I Believe that “PRN” should be required with all “PO” formulations due to GI, Cardiac and Renal effects

Prostanoids and Pain

Injury

Phospholipids

Phospholipase → Arachidonic Acid

COX (prostaglandin H Synthase)

→ PGG2

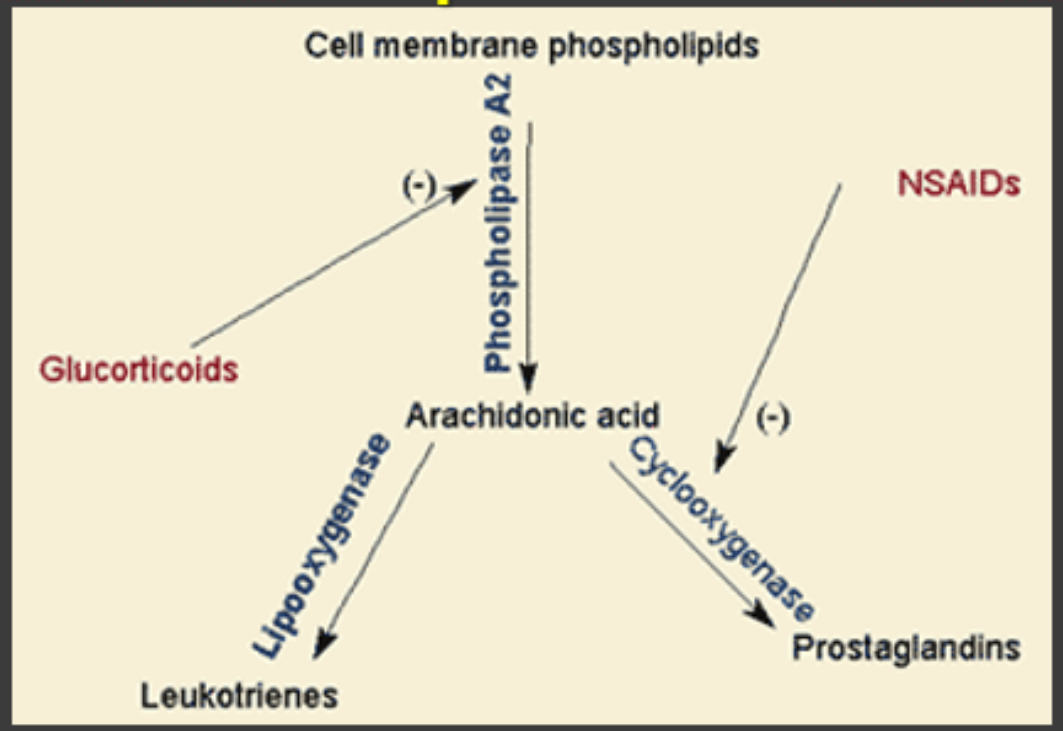
PGH2 ↓

other Prostanoids

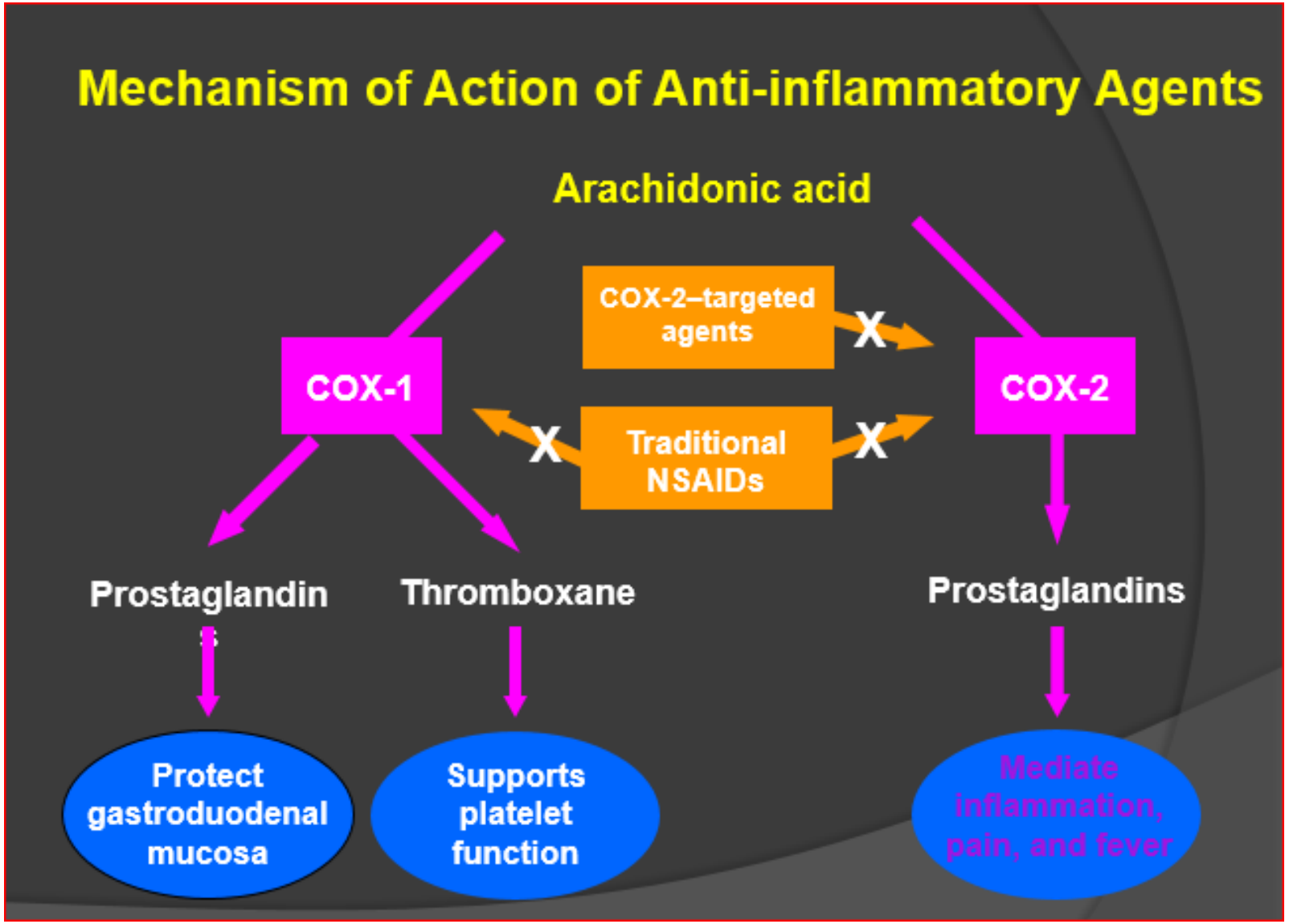
PGD2, PGE2, PGF2, PGI2, TXA2

(Inflammatory mediators, sensitizing factors, cytoprotective agents)

Glucocorticoids are potent anti-inflammatories

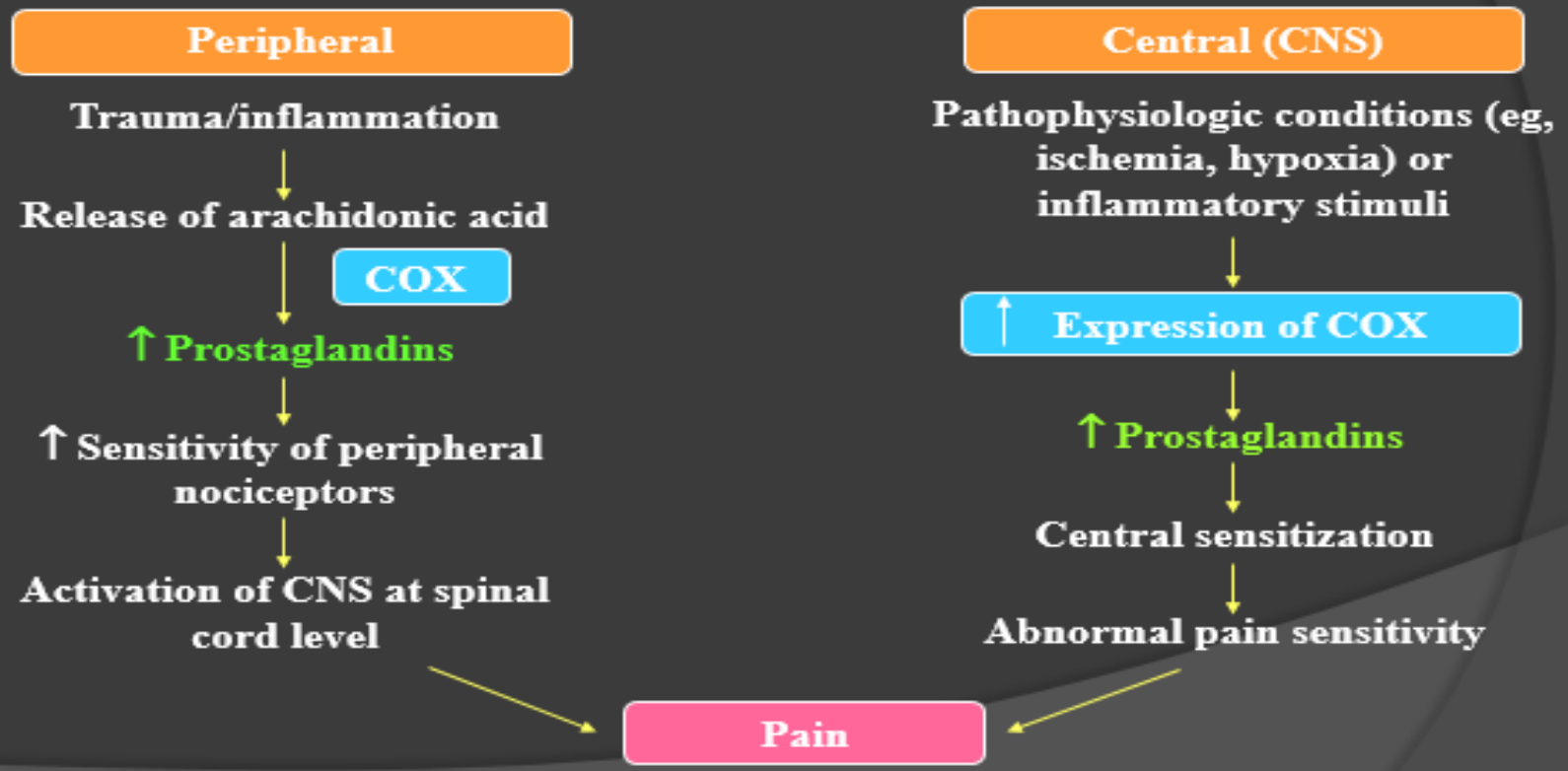


Primary anti-inflammatory mechanism is Lipocortin-1 synthesis. Lipocortin-1 suppresses PA2, blocking Eicosanoid production, & suppressing Prostaglandins & Leukotrienes.


Mechanism of Action of Anti-inflammatory Agents
Arachidonic acid
COX-2–targeted agents
X
COX-1
COX-2
X
Traditional NSAIDs
X
Prostaglandin
Thromboxane
Prostaglandins
Protect gastroduodenal mucosa
Supports platelet function
Mediate inflammation, pain, and fever

A Working Hypothesis

Role of Prostaglandins in Pain



Yaksh et.al; Cancer Invet;16(7) 1998;509-527 Malmberg; Science;257;1992;1276-79; Smith et.a. Proc Natal Acad Sci;95;1998; 13313-13318;

NSAID's

- Effective in mild to moderate pain
  - Dental
  - Minor orthopedic procedures, strains, sprains
  - Ambulatory surgery
  - Postpartum pain
- Benefit
  - Lack opioid adverse effects including respiratory depression
- Most commonly used drug class in US 70 million prescriptions per year
  - Served as analgesics, anti-inflammatory, & antipyretic medicines since 1898
  - ***9-10% of prescriptions worldwide are NSAIDs***
  - ***1-2% of U.S. population uses prescriptions daily***

J. Joris. *Acta Anaesth. Belg.* 1996:47;115-123

FDA Strengthens NSAID Warning of Heart Attack and Stroke Risk for ...

www.fda.gov › consumers › consumer-updates › fda-st...
Jun 9, 2015 - FDA is strengthening labels warning that nonsteroidal anti-inflammatory drugs (NSAIDs), used for the temporary relief of pain and fever, can ...

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) | FDA
www.fda.gov › drugs › nonsteroidal-anti-inflammatory...
Oct 5, 2016 - Examples of prescription NSAIDs include ibuprofen, naproxen, ... FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory ...

FDA strengthens warning that NSAIDs increase heart attack ...
www.health.harvard.edu › blog › fda-strengthens-warni...
Jun 27, 2019 - The FDA has strengthened its warning that NSAIDs like ibuprofen and naproxen increase heart attack and stroke risk.

FDA warns of heart attack and stroke risks from Ibuprofen ...
www.businessinsider.com › fda-warns-of-heart-attack-a...
Nov 16, 2017 - The FDA updated its warnings for the category of drugs, NSAIDs, based on more evidence of the increased risk. Some of the most common ...

NSAID Drug Interactions

1. Most (if not all) NSAIDs can increase the anticoagulant effect of WARFARIN: displacement of warfarin from plasma albumin and the subsequent inhibition of warfarin metabolism and elimination

2. Potentially all NSAIDs can blunt the diuretic actions of THIAZOLE by competing for the active secretion proximal tubule.

3. May enhance the toxicity of METHOTREXATE (a cancer drug) by blocking its tubular secretion.

4. May reduce the renal elimination of Li^+ ions (Manic depression disorders) and cause a significant elevations of the plasma [Li^+]

5. May interfere with the anti-hypertensive actions of beta-blockers, diuretics, and ACE-inhibitors.

6. NOV2004 study: In high risk patients with recent ischemic stroke or transient ischemic attacks, adding aspirin to clopidogrel (PLAVIX; an antiplatelet agent) increased the risk of life-threatening or major bleeding events (Diener et al. 2004 *Lancet)*

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

  Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

  Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - increasing doses of NSAIDs
  - longer use of NSAIDs
  - smoking
  - drinking alcohol
  - older age
  - poor health
  - advanced liver disease
  - bleeding problems

NonSteroidal Anti-Inflammatory Drugs (NSAIDs)

Realistic expectations-

- *PAIN AND/OR INFLAMMATION BENEFIT- BALANCE WITH RISK- PRN" FOR ORAL'S*

NSAIDs increase the risk of fatal adverse reactions including bleeding, ulcers, and perforation of the stomach or intestines.

--These events can occur at any time during treatment & without warning symptoms (60-80% no pain while GI bleeding). Never give more than 1-2 months in a row & Celebrex also has a risk of GI bleed it is just less than NSAIDs
--**Is the patient on a blood thinner already?**
--Elderly patients are at greater risk for these adverse events.
--**Negative Renal effects**= Does patient have other risks? DM? ACEI, Diuretics?
--NSAIDs, besides aspirin, increase the risk of a potentially fatal heart attack or stroke = The FDA warned that "those serious side effects can occur as early as the first few weeks of using an NSAID, & the risk might rise the longer people take NSAIDs". "There is no period of use shown to be without risk,"

NSAID WARNING- RISK FACTORS. ALWAYS STAY HYDRATED- GFR ? DM? ON ACEI,DIURETIC?

NSAID Therapeutics

- When used as analgesics, these drugs usually are effective only against pain of low-to-moderate intensity.
- Although their maximal effects are much lower, they lack the unwanted effects of the opioids on the CNS (development of physical dependence and respiratory depression).
- NSAIDs reduce body temperature (antipyretic effect)
- Anti-inflammatory: treatment of musculoskeletal disorders (Rheumatoid arthritis, osteoarthritis, ..).

Oral NSAIDs strongly recommended for patients with knee, hip, and/or hand osteoarthritis—just not everyday as you will have a GI bleed for certain!

Table II: Topical Diclofenac Products and Dosing in Osteoarthritis

Product	Formulation and Strength	Dosing
Voltaren gel	1% gel	Upper extremities: 2 g four times daily Lower extremities: 4 g four times daily Maximum overall joints: 32 g/day
Flector patch	1.3% patch	1 patch every 12 hours
Pennsaid solution	1.5% solution	40 drops to each knee, four times a day
Pennsaid pump	2% pump	2 pump actuations to each knee, twice a day

References 9-11

Who this may help: Stiffness, trouble bending, hands, joints.

How many of your patients actually use the gel BID-QID?

TOPICAL OPTIONS

- OTC NOW = TOPICAL NSAIDS STRONGLY RECOMMENDED FOR PATIENTS WITH KNEE OA; CONDITIONALLY RECOMMENDED FOR THOSE WITH HAND OA

VOLTAREN GEL

- Lower extremities: Apply the gel (4 g) to
- the affected area 4 times daily. Do not
- apply more than 16 g daily to any one
- affected joint of the lower extremities.
- □
- Upper extremities: Apply the gel (2 g) to the
- affected area 4 times daily. Do not apply
- more than 8 g daily to any one affected
- joint of the upper extremities.

New IV version of meloxicam (*Anjeso*).

Once-daily IV analgesic for managing post-op pain

Other injectable NSAIDs: diclofenac (*Dyloject*), ibuprofen (*Caldolor*) and ketorolac(Toradol). All 4 approved for pain...alone or in combo with other analgesics.

In post-op trials, giving IV meloxicam instead of placebo only reduces opioid use by about 2 doses over 48 hours.

IV meloxicam's onset of analgesia takes 2 to 3 hours...versus about 1 hour or less with other IV NSAIDs.

IV meloxicam's pain relief wears off after about 18 hours...creating a gap in analgesia at the end of the dose interval.

IV ketorolac or ibuprofen cost about $2/dose...vs about $16 for diclofenac or $94/dose for meloxicam.

And ketorolac can be given IV push (Usually IM) ...like diclofenac or meloxicam. But ibuprofen requires IV infusion over at least 30 min.

Caution with any NSAID in patients with renal dysfunction...high CV risk...or GI risk factors, such as a previous ulcer or taking antithrombotics or corticosteroids.

Table 1. Available Formulations of Parenteral NSAIDs Used for Pain Control

Drug (Brand)	Formulations	Approved Indication(s)
Ketorolac tromethamine (Toradol)	10 mg/mL 30 mg/mL	Short-term management of moderately severe acute pain
Ibuprofen (Caldolor)[a]	400 mg/4 mL vial 800 mg/8 mL vial	Mild-to-moderate pain, moderate-to-severe pain as an adjunct to opioids

[a] *Also indicated for fever reduction in adults.*
Source: References 8, 9.

Meloxicam As a Molecule Has Analgesic and Anti-inflammatory Activity

Meloxicam exhibits "preferential COX-2" activity based on in vitro studies

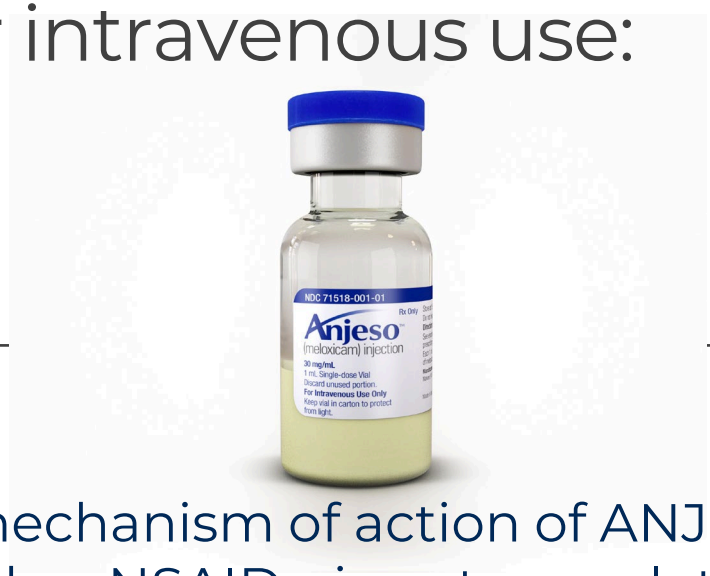
Oral meloxicam was approved in 2000[1]

- Indicated for use chronic pain conditions, including osteoarthritis and rheumatoid arthritis†
- Dosing ranges from 7.5 mg to 15 mg daily
- T_{max} is 5 to 6 hours after dosing

ANJESO uses NanoCrystal® Technology to improve meloxicam solubility[3,‡]

- Permits IV administration and immediate systemic availability
- Suitable for use in the surgical setting

ANJESO®(meloxicam IV) injection for intravenous use: Indication and Usage



INDICATION

ANJESO® (meloxicam) injection is indicated for use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics.

Limitation of Use: Because of delayed onset of analgesia, ANJESO® alone is not recommended for use when rapid onset of analgesia is required.

ANJESO® was approved February 2020.

The mechanism of action of ANJESO, like other NSAIDs, is not completely understood, but involves inhibition of both COX-1 and COX-2 pathways. ANJESO has a preferential COX-2 activity. COX-2 activity is based on in vitro data, not clinical trial data.[2]

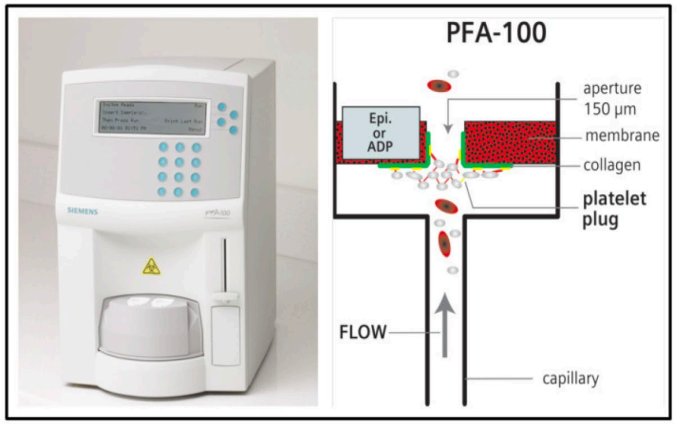
When initiating ANJESO, monitor patient pain response. If patient experiences inadequate analgesia during the 24-hour dosing interval, consider adding a short-acting, non-NSAID, immediate-release analgesic.[1]

1. ANJESO ® [package insert]. Malvern, PA: Baudax Bio, Inc; 2020. 2. Warner TD et al. *Proc Natl Acad Sci USA*. 1999

Formation of Platelet Plug in Ex Vivo Study

Ex-Vivo Assessment of Effects of Meloxicam on Platelet Function

- No significant prolongation in Closure Time for meloxicam IV vs. untreated control
- Significant prolongation in Closure Time for ketorolac vs. untreated control



CT= Closure Time

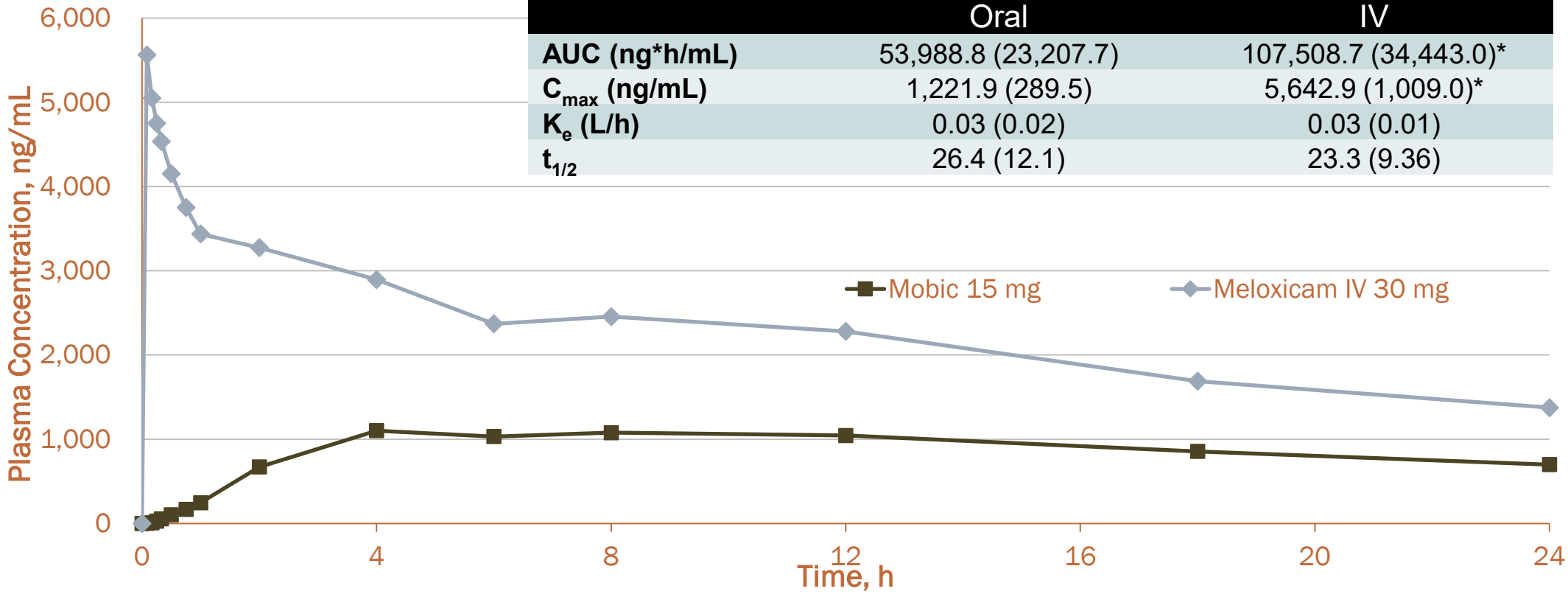
CEPI Reagent	Untreated Control	Ketorolac IV		Meloxicam IV			
		2.5 µg/mL	5 µg/mL	5 µg/mL	10 µg/mL	15 µg/mL	20 µg/mL
		~ 15 mg	~ 30 mg	~ 30 mg	~ 60 mg	~ 90 mg	~ 120 mg
LS Mean (SE) Closure Time	90.5 (16.544)	180.87 (16.544)	143.38 (16.544)	101.75 (16.544)	95.13 (16.544)	104.00 (16.544)	104.63 (16.544)
p-value vs. Untreated control		0.0003	0.0257	0.6252	0.8406	0.5580	0.5400
p-value vs. 2.5 µg/mL ketorolac			0.1084	0.0012	0.0005	0.0017	0.0018
p-value vs. 5 µg/mL ketorolac				0.0757	0.0408	0.0923	0.0974

Jahr J et al, *Clinical Pharmacology in Drug Development* 2020

* Additional clinical data is needed to evaluate clinical benefit

Meloxicam IV Pharmacokinetics: Single Dose (30 mg IV vs 15 mg oral)

	15 mg Oral	30 mg IV
AUC (ng*h/mL)	53,988.8 (23,207.7)	107,508.7 (34,443.0)*
C_{max} (ng/mL)	1,221.9 (289.5)	5,642.9 (1,009.0)*
K_e (L/h)	0.03 (0.02)	0.03 (0.01)
$t_{1/2}$	26.4 (12.1)	23.3 (9.36)

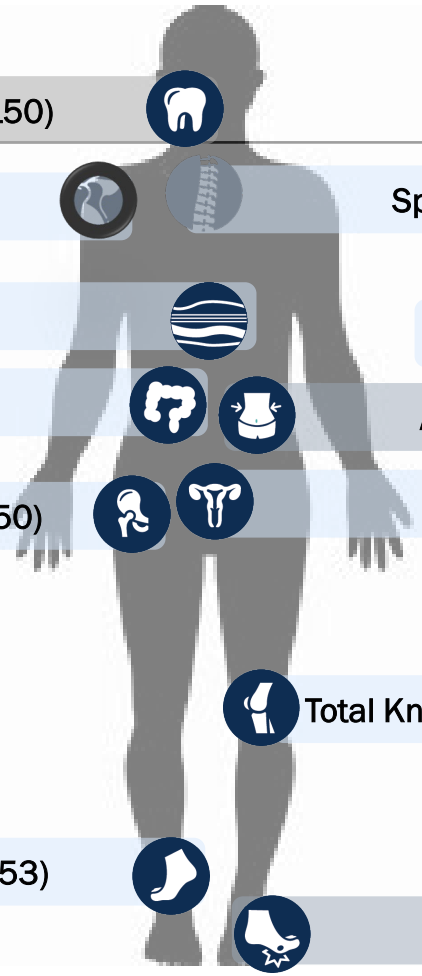


AUC=area under the curve; C_{max}=maximum concentration; K_e=elimination rate constant; $t_{1/2}$=elimination half-life;

Data on file. Baudax Bio, Inc.

Apseloff, 2009

Meloxicam IV Was Studied in Multiple Procedures



Phase 2 Studies

Phase 3 Major Surgery Safety

Phase 3 Efficacy and Safety

Phase 3b

Third Molar Extraction (n=150)

Shoulder (n=13)

Spinal/Head/Neck (n=11)

Other Soft Tissue (n=128)

Abdominoplasty (n=32)

Colon Resection Surgery (N =

Gastrointestinal (n=26)

Abdominoplasty (n=110)

Total Hip Replacement (n=50)

Gynecologic (n=68)

Hysterectomy (n=300)

Total Knee Replacement (n=117)

Total Knee Replacement (N =

Bunionectomy (n=40)

Complex Foot & Ankle (n = 53)

Bunionectomy (n = 100)

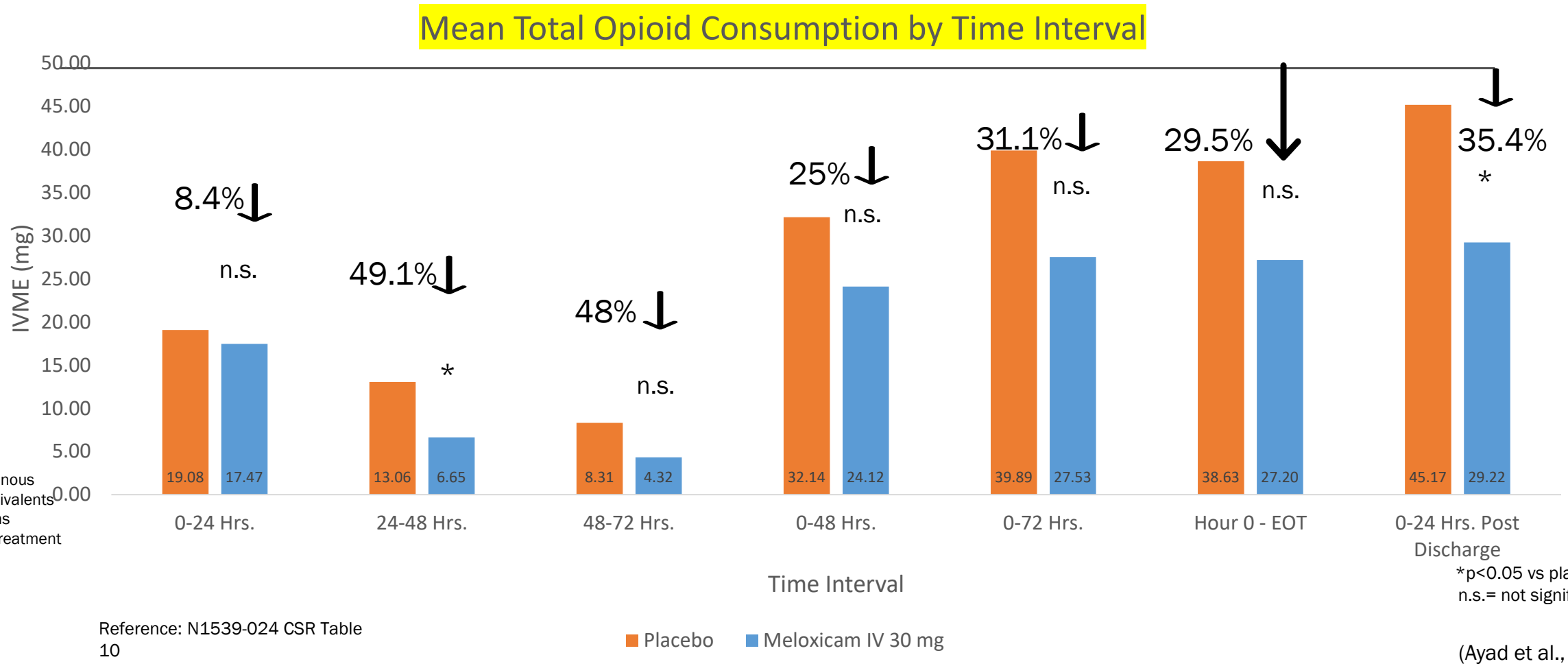
Adverse Events in Postoperative Studies

Adverse Events Occurring in ≥3% of Patients Treated With Meloxicam IV 30 mg, From 7 randomized, double-blind, placebo-controlled postoperative studies

Event Type	n (%) of Subjects	
	Meloxicam IV 30 mg N=910	Placebo N=296
Subjects with ≥1 AE	**497 (54.6)**	**296 (57.3)**
Nausea	189 (20.8)	131 (25.3)
Constipation	61 (6.7)	25 (4.8)
Headache	51 (5.6)	54 (10.4)
Vomiting	42 (4.6)	38 (7.4)
Dizziness	32 (3.5)	25 (4.8)
Pruritus	31 (3.4)	15 (2.9)

AE=adverse event
Data on file. Baudax Bio, Inc.

Phase 3b: Colorectal Surgery



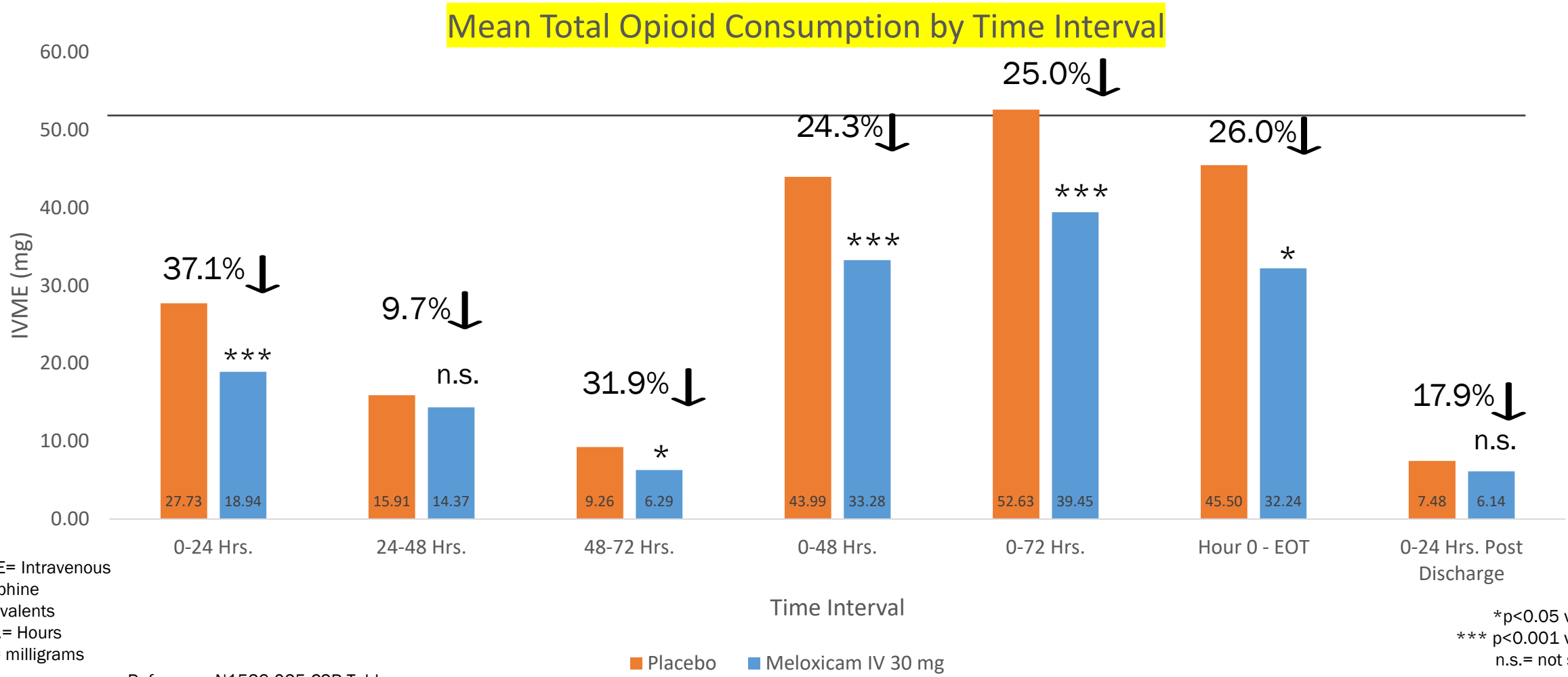
IVME= Intravenous Morphine Equivalents
mg= milligrams
EOT= End of treatment
Hrs..= Hours

*p<0.05 vs placebo
n.s.= not significant

Reference: N1539-024 CSR Table 10

(Ayad et al., 2019)

Phase 3b: Total Knee Arthroplasty



IVME= Intravenous Morphine Equivalents
Hrs..= Hours
mg= milligrams

Reference: N1539-025 CSR Table 14

*p<0.05 vs placebo
*** p<0.001 vs placebo
n.s.= not significant

(Berkowitz R, Boyer P, MelsonT, Sharp K , 2019

Adverse Events Comparable Between ANJESO and Placebo[1]

Subjects with ≥ 1 TEAE	ANJESO, n (%) (n=538)	Placebo, n (%) (n=183)
Most Common Events (≥3%)	339 (63)	119 (65)
Nausea	123 (22.9)	51 (27.9)
Constipation	51 (9.5)	17 (9.3)
Vomiting	27 (5.0)	14 (7.7)
GGT increased	21 (3.9)	5 (2.7)
Pruritus	21 (3.9)	10 (5.5)
Headache	20 (3.7)	12 (6.6)
Anemia	18 (3.3)	4 (2.2)
Dizziness	15 (2.8)	8 (4.4)
ALT increased	11 (2.0)	7 (3.8)

ANJESO showed no increased rate of AEs in patients >65 years of age with mild renal impairment (GFR 60-89 mL/min/1.73 m^2).[2]

Precautions with NSAID's

1. Surgical bleeding that may be affected by platelet dysfunction--**make sure your patients are off them 3-7 days prior!**
2. GI sensitivity, GI bleeding
3. Renal insufficiency can worsen function
4. NSAID allergy
5. AGE
6. Other meds :diuretics, herbals, SSRI's

Mechanism of action for tests: "Acetaminophen reduces heme at the peroxidase site-"

Acetaminophen

- **Trade Names:** generic, Tylenol ®, also known as **paracetamol** in Europe (Wikipedia: paracetamol)
- **Drug Class:** Analgesic & Antipyretic; but it is not a NSAID!
- **Mechanism of Action (Debated):**
  - ***"COX-associated Peroxidase Hypothesis"***:
    - The "prevailing" hypothesis is that acetaminophen acts as a reducing agent to inhibit a secondary peroxidase step involved in prostanoid synthesis by cyclooxgenase (COX-1 & COX-2) enzymes (see Figure 1). **Because it inhibits the peroxidase reaction, its inhibitory effects are surmounted in the presence of high levels of lipid hydroperoxides that are produced by activated leukocytes & platelets. This prevents acetaminophen from being effective in sites of inflammation or activated platelets**. Hence acetaminophen exerts little or no anti-platelet or anti-inflammatory effects. In contrast, because hydroperoxide levels are relatively low in vascular endothelial cells and neurons, acetaminophen is able to exert antipyretic and analgesic effects by blocking the production of prostaglandins in these locations (Aronoff et al, 2009).

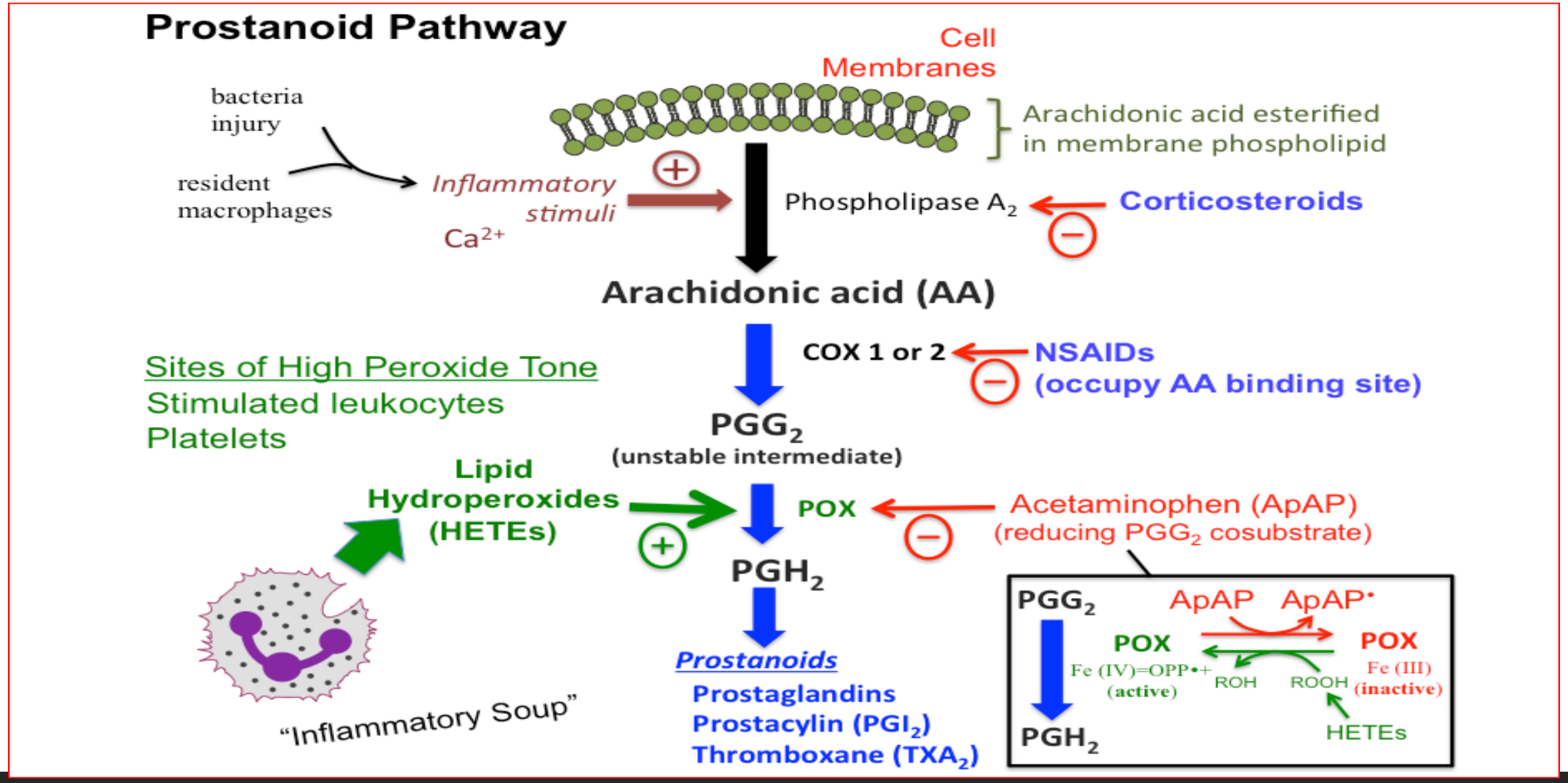
In 1960, “APAP” acetaminophen (paracetamol) was introduced in the United States as a nonprescription analgesic and antipyretic.

(OTC) nonprescription drug : Internal Analgesic, Antipyretic, and Antirheumatic Drug

FDA changed the recommended dose of the Acetaminophen to **325 mg tablets in any prescription.** The **maximum daily dose of Acetaminophen is 2800 mg**.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3585765/

Studies have shown that acetaminophen lacks peripheral anti-inflammatory properties. It may be that acetaminophen inhibits the COX pathway in the central nervous system but not peripheral tissues.



The IV formulation of acetaminophen is primarily for in-hospital use. The oral and rectal formulations of acetaminophen are more widely administered for fever reduction and the temporary relief of minor aches, pains, and headache. Ofirmev® (acetaminophen) injection is indicated for

1. the management of mild to moderate pain in adult and pediatric patients 2 years and older

2. the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older

3. the reduction of fever in adult and pediatric patients.

A number of studies have found similar efficacy with oral acetaminophen versus IV acetaminophen at substantial cost savings.

In 2011, the FDA required the labeling of all acetaminophen-containing prescription products to add a boxed warning regarding **hepatotoxicity** risk

Acetaminophen-related hepatotoxicity is the l**eading cause of acute liver failure globally.** Some patients may be at an increased risk for acetaminophen-related liver toxicity including the elderly, those with concurrent hepatic disease, and those who consume 3 or more alcoholic drinks daily

FDA Warning : Alerting consumers that the use of acetaminophen may cause severe skin reactions. This guidance is intended to apply to single- and combination-ingredient acetaminophen-containing products marketed: Risk of rare but serious skin reactions. These skin reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, can be fatal. The DSC explained that reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain acetaminophen.

FDA advised health care professionals to be aware of this rare risk and consider acetaminophen, along with other drugs already known to have such an association, when assessing patients with potentially drug-induced skin reactions. FDA also advised that anyone who develops a skin rash or reaction while using acetaminophen or any other pain reliever/fever reducer should stop taking the drug and seek medical attention right away.
https://www.fda.gov/files/drugs/published/Recommended-Warning-for-Over-the-Counter-Acetaminophen-Containing-Drug-Products-and-Labeling-Statements-Regarding-Serious-Skin-Reactions.pdf

Acetaminophen and Pregnancy

-2015: The FDA reviewed the possible risks of analgesic medication use during pregnancy due to reports questioning their safety. Regarding acetaminophen, concerns arose when a cohort study concluded that maternal use during pregnancy was associated with an **increased risk of attention deficit hyperactivity disorder** (ADHD)-like behaviors and hyperkinetic disorders in children. However, the FDA concluded that the studies included in their review had potential design limitations and conflicting results. The FDA continues to **recommend that patients & clinicians continue to carefully weigh the risks & benefits** of prescription & OTC pain relievers, including acetaminophen, during pregnancy.

-2022: 29 observational studies, increase in attention deficit hyperactivity disorder, autism spectrum disorder, language delays, lower IQ, cerebral palsy, oppositional defiant disorder, decreased executive function and conduct disorders.

Advil Dual Action contains two medications that treat pain: ibuprofen and acetaminophen. It has the following amounts of each medication in a single pill:
Ibuprofen: 125 mg
Acetaminophen: 250 mg

March 12, 2019

Association of Tramadol With All-Cause Mortality Among Patients With Osteoarthritis:

The biological mechanisms linking tramadol to mortality are unclear. Tramadol may activate μ opioid receptors & inhibit central serotonin & NE reuptake, & the latter may result in a unique adverse effect on the neurological system (i.e., serotonin syndrome and seizures). Tramadol may also increase the risk of postoperative delirium, which tends to increase mortality. Fatal poisoning or respiratory depression may occur when tramadol users consume alcohol or use tramadol with other central nervous systems depressants.

Furthermore, tramadol may increase the risk of hypoglycemia, hyponatremia, fracture, or fall, thus leading to an increased risk of death. *Among patients aged 50 years and older with osteoarthritis, initial prescription of tramadol was associated with a significantly higher risk of mortality over 1 year of follow-up compared with commonly prescribed NSAIDs, but not when compared with codeine. However, these findings may be susceptible to confounding by indication, and further research is needed to determine if this association is causal.*

4 S's—seizures, serotonin syndrome, sedation, and suicide risks

https://jamanetwork.com/journals/jama/fullarticle/2727448

TRAMADOL: SCHEDULE IV CONTROLLED SUBSTANCE, EFFECTIVE AUGUST 18, 2014. Effective August 18, 2014, tramadol and products containing tramadol will be classified as Schedule IV controlled substances pursuant to 21 CFR 1308.

Tramadol produces **QTc interval prolongation** in good correlation with plasma drug concentrations; renal failure is a risk factor for higher concentration and QT prolongation by tramadol.

Tramadol Induced QTc-Interval Prolongation: Prevalence, Clinical Factors and Correlation to Plasma Concentrations
Curr Drug Saf
. 2016;11(3):206-14. doi: 10.2174/1574886311666160225150405.

Tramadol (*Ultram ER*) and in immediate-release tablets alone *(Ultram*)
Extended-release tablets are available as:
100 mg tablets: Round, convex, white to off-white, non-scored, imprinted with “100” over “ER” on one side in black ink
200 mg tablets: Round, convex, white to off-white, non-scored, imprinted with “200” over “ER” on one side in black ink
300 mg tablets: Round, convex, white to off-white, non-scored, imprinted with “300” over “ER” on one side in black ink

The initial dose of Ultram ER is 100 mg once daily.
Patients Currently on Tramadol Immediate-Release (IR) Products
Calculate the 24-hour tramadol IR dose and initiate a total daily dose of Ultram ER rounded down to the next lower 100 mg increment. The dose may subsequently be individualized according to patient need.

Tramadol hydrochloride extended-release (*Ryzolt* – Purdue) for treatment of moderate to moderately severe chronic pain in adults.

ConZip™ is available in 100 mg, 200 mg and 300 mg extended-release capsules.

100 mg Capsules: White capsule imprinted with blue ink “G 252” on cap and “100” between lines on the body
200 mg Capsules: White capsule imprinted with violet ink “G 253” on cap and “200” between lines on the body
300 mg Capsules: White capsule imprinted with red ink “G 254” on cap and “300” between lines on the body
ConZip™ is an extended-release formulation intended for once a day dosing in adults aged 18 years and older. The tablets must be swallowed whole with liquid and must not be split, chewed, dissolved or crushed. Chewing, crushing or splitting the tablet could result in the uncontrolled delivery of tramadol, in overdose and death

(*Ultracet*) *Tramadol* HCl 37.5mg, *acetaminophen* 325mg; tabs.
= Tramadol combined with acetaminophen=The initial *dose* of *ULTRACET* is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

Ultram ER and Conzip (tramadol ER)

Age 18 years of age or older

Patient must have the following:

Moderate to severe pain requiring daily, around-the-clock long term opioid treatment

Tramadol = acts as an antidepressant because it increases levels of serotonin in the brain, which elevates mood. Elevates serotonin & can cause seizures.

Some ethnic groups may metabolize more efficiently

Dependent on users' genetics= Those from Africa, the Middle East and parts of Asia.
Studies suggest **nearly 30% of North Africans metabolize tramadol to the most active potency compared with about 1 percent of northern Europeans.**

In a large population-based cohort, the initiation of *tramadol* was associated with an at-least 2-fold increased risk of hospitalization for *hyponatremia*

Tramadol produces **QTc** interval **prolongation** in good correlation with plasma drug concentrations; renal failure is a risk factor for higher concentration and **QT prolongation** by **tramadol**.

- *OPIOID-SPARING BENEFITS OF ADJUVANTS ?*

Tramadol

Opioid use booming as tramadol crisis emerges in Africa – U.N. drug report
Jun 25, 2019
VIENNA (Reuters) – Synthetic opioid use is booming, the United Nations said on Wednesday in a worldwide drug report that showed deaths in the United States from overdoses still rising and a "crisis" of tramadol use emerging in parts of Africa.

Cities with high tramadol abuse have reported increasingly high rates of traffic accidents. In Garoua, Cameroon, hospitals can trace **80 percent of all traffic accidents resulting in hospital visits to tramadol, suggesting that at least half of adults in the city use tramadol.** To make it even more apparent how dire tramadol addiction has become, hospital staff reported that people waiting for patients outside of the hospital gates would start convulsing, the sign of a tramadol overdose. In some countries, tramadol deaths outnumber heroin deaths.

- *OPIOID-SPARING BENEFITS OF ADJUVANTS ?*

Anticonvulsants

- Depress abnormal neuronal discharges
- Raise threshold for propagation of neural impulse
- ***Used in neuropathic pain/Headaches***
- Initial dose should be low, at bedtime, & titrate up to desired effect

Clinical Pearl: I have patients start with Dinner and/or bedtime. Less need for "a.m." dosing- Less morning sedation. Medication is still in CNS from HS dose!

⦿ **Carbamazepine** (Tegretol®) FDA approved for **Trigeminal Neuralgia**

- Reduces both Na+ and K+ conductance
  - Slows the recovery of voltage-gated Na+ channels
- ***Thrombocytopenia, leukopenia, hyponatremia***
- ***Aplastic anemia (1:200,000), rash***
- Carbamazepine also increases the metabolism of the hormones in birth control pills and can reduce their effectiveness, potentially leading to unexpected pregnancies. As a drug that induces **cytochrome P450 enzymes**, it **accelerates elimination of many benzodiazepines and decreases their action.**

⦿ **Valproic Acid** (Depakote ER®)

- Approved for Migraine
- Mechanism inhibits catabolism of GABA by interfering with GABA transaminase & increases synaptic release of GABA, resulting in an increase in GABA levels
- SE include ataxia, rash, alopecia, appetite stimulation...weight gain
  - ***Hepatic failure (1:50,000)***
  - ***Pancreatitis: 364 MDs found 54 cases over past 30 years***
  - ***Teratogen associated with spina bifida***

⦿ **Lamotrigine** (Lamictal®) reported useful in neuropathic pain states (sciatica, HIV peripheral neuropathy) & in post stroke pain states.

- Inhibits voltage-gated Na^+ channels
  - Also suppresses glutamate release and serotonin reuptake
- Initial dose 25-50mg/day up to 900mg BID or TID
  - ***SE include diplopia, drowsiness, rash (10% of pts)***
  - ***Black box warning for SJS with Valproic Acid –Do not use combination for pain conditions!***
  - ***Safety Announcement. A U.S. Food and Drug Administration (FDA) review of study findings showed a potential increased risk of heart rhythm problems, called arrhythmias, in patients with heart disease who are taking the seizure and mental health medicine lamotrigine (Lamictal).Mar 31, 2021***

⦿ **Topiramate** (Topamax®) (used since 1997) –Approved for migraine

- Unique structure, unlike any of the other AEDs
  - Potentiates central GABA levels
  - AMPA kainate receptor blocker (AMPA kainate preserve axon function and structure)
  - Weak carbonic anhydrase inhibitor
- Initial dose 25mg hs, up to 200mg TID Dosed before dinner (meals) / hs-helps sleep!
  - ***SE include kidney stones, anhydrosis, glaucoma, weight loss! altered thinking***
  - ***("dopamax", "blonde in a bottle") NOT POLITICALLY CORRECT!***

⦿ **Phenytoin** (Dilantin®), no sedation like many other AED's (RARELY USED FOR Pain Management)

- Mechanism similar to carbamazepine, used for partial & generalized seizures
- Narrow therapeutic window
- ***Stevens-Johnson syndrome, birth defects fetal hydantoin syndrome***
- ***Gingival hyperplasia 10-20%***

Phenytoin is an inducer of the CYP3A4 and CYP2C9 families of the P450 enzyme responsible for the liver's degradation of various drugs.

Cytochrome P450

Phenytoin is an inducer of the CYP3A4 and CYP2C9

Carbamazepine is an inducer of CYP3A4

Table 2. Common Drugs Used in Pain and Their Metabolism Pathway			
CYP2D6	**CYP2C9**	**CYP3A4/5**	**CYP2B6**
Amitriptyline	Celecoxib	Codeine	Methadone
Codeine	Flurbiprofen	Diazepam	
Desipramine	Ibuprofen	Fentanyl	
Diazepam	Meloxicam	Hydrocodone	
Hydrocodone	Piroxicam	Oxycodone	
Imipramine		Methadone	
Methadone			
Nortriptyline			
Oxycodone			
Tramadol			
Venlafaxine			

Like other antiepileptic drugs, TOPAMAX® may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

HEADACHES:

Divalproex sodium, valproate sodium, and topiramate have established efficacy in migraine prevention.

Carbamazepine is possibly effective in migraine prevention.

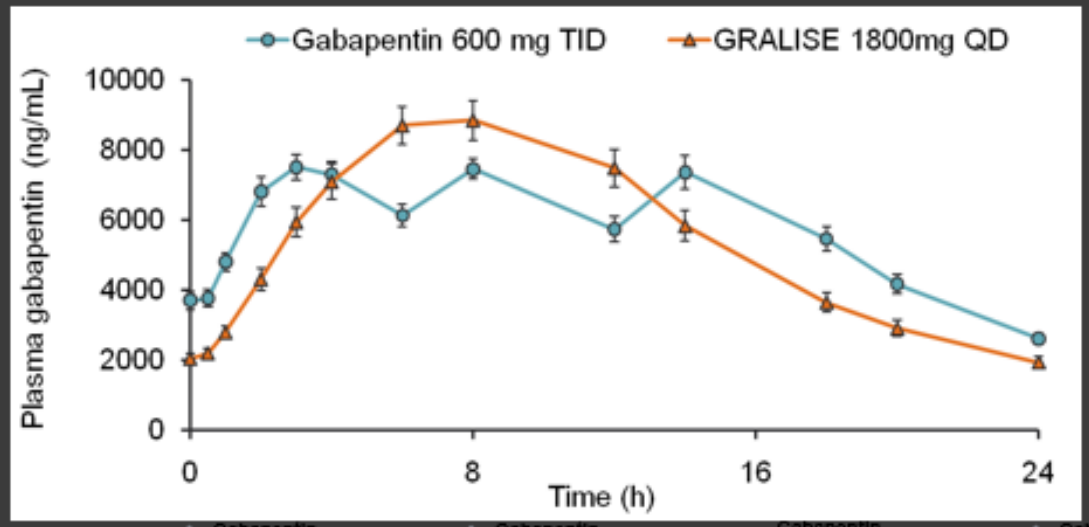
Verapamil treatment of choice for prevention of cluster headaches.

BETA BLOCKERS (propranolol) treatment of choice for prevention of migraine headaches.

- **Gabapentin** (Neurontin®) FDA approved for PHN, studied in many different neuropathic pain states Zoster, RLS & Headaches.
  - Mechanism of action unclear-was developed as a GABA analog
    - ***Influences a central voltage dependent L-type Ca^{2+} channel***
  - Initial dose 100mg-300mg qhs, **increased ONLY IF TOLERATED** to 3600mg/day
  - SE include: Resp. depression, drowsiness, nausea, fatigue,
  - Peripheral edema=Weight gain
  - Renally excreted, no drug-drug interactions, t1/2 6 hrs.

- Pregabalin (Lyrica®) C-V CONTROLLED SUBSTANCE Not on "PDMP" in California ! FDA approved for Fibromyalgia, Diabetic Neuropathy, & PHN, studied in many different neuropathic states and Headaches.
  - Mechanism of action--**An $\alpha 2\delta$ subunit calcium channel blocker; reduces release of neurotransmitters; not active at GABA receptors;** Analog of gabapentin
  - Initial dose 50-75mg qhs, increased ONLY IF TOLERATED to 600mg, linear pharmacokinetics
    - SE include drowsiness, fatigue, Weight gain, Resp. depression
    - Renally excreted, t1/2 6.3 hrs.

Steady State Pharmacokinetics (Day 5)



PK Parameters	GRALISE Once Daily	Gabapentin TID
AUC (ng·hr/mL)	132,808 ± 34,701	141,301 ± 29,759
Cmax (ng/mL)	9,585 ± 2,326	8,536 ± 1,715
Cmin (ng/mL)	1,842 ± 654	2,588 ± 783

Gordi, et al. *Clin Ther.* 2008;30:909-916.
* Relative to most recent dose.
GRALISE US PI 2011.

Gralise need to eat meal 5-6 PM peaks 9 hours later—additional 1 hour of sleep

Gabapentinoids:

Potential for misuse and abuse with gabapentin and pregabalin.

Since approval, usage of both agents has expanded considerably and, in conjunction with the opioid epidemic in the United States, there have been increasing case reports and case series of inappropriate use.

The majority of these reports have revealed particular concern for patients with a history of substance abuse.

Clinicians considering prescribing gabapentinoids should carefully evaluate each patient for a previous history of drug abuse and be able to promptly identify signs of potential abuse and misuse

Alabama Designates Gabapentin as a **Schedule V Drug**. Effective November 18, 2019, Gabapentin is a Schedule V Controlled Substance in Alabama. Though Gabapentin is not a controlled substance at the federal level, Alabama joins a growing list of states that have reclassified the drug as a controlled substance in the past year

The Abuse Potential of Gabapentin & Pregabalin

In the European Union, pregabalin has also been indicated for generalized anxiety disorder.
From 2012 to 2016 in the United States, gabapentin prescribing increased by 64%. In 2017, 68 million prescriptions of gabapentin were dispensed, making gabapentin the 10th most commonly prescribed medication. Gabapentinoids may have their own inherent abuse potential.
Pregabalin has been classified as a Schedule V controlled substance since its release to the market in 2005, *indicating that it has potential for abuse*. The first marketed medication in this class, gabapentin, is not currently classified as a controlled substance in most states, however, its abuse potential is still being investigated. Kentucky, Michigan, and Tennessee (Others?) have reclassified gabapentin as a Schedule V controlled substance.

Pregabalin (gabapentinoids) offer prescribers an opioid-alternative treatment for certain types of neuropathic pain:

INDICATION	Dosing Regimen	Maximum Dose
DPN Pain (2.2)	3 divided doses per day	300 mg/day within 1 week
PHN (2.3)	2 or 3 divided doses per day	300 mg/day within 1 week. Maximum dose of 600 mg/day.
Fibromyalgia (2.5)	2 divided doses per day	300 mg/day within 1 week. Maximum dose of 450 mg/day.
Neuropathic Pain Associated with Spinal Cord Injury (2.6)	2 divided doses per day	300 mg/day within 1 week. Maximum dose of 600 mg/day.

- Dose should be adjusted in adult patients with reduced renal function. (2.7)

DOSAGE FORMS AND STRENGTHS

- Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg. (3)
- Oral Solution: 20 mg/mL. (3)

ONCE-DAILY LYRICA CR

LYRICA CR IS AVAILABLE IN 3 DOSAGE STRENGTHS.


82.5 mg


165 mg


330 mg

How is LYRICA CR different?	LYRICA PREGABALIN	LYRICA CR
How often do you take it?*	*Diabetic Nerve Pain: 3 times a day* *Pain After Shingles: 2-3 times a day*	*Once a day*
Recommended starting dose (daily total)	*Diabetic Nerve Pain: 150 mg/day* *Pain After Shingles: 150 mg/day*	*Diabetic Nerve Pain: 165 mg/day* *Pain After Shingles: 165 mg/day*

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LYRICA CR safely and effectively. See full prescribing information for LYRICA CR.

LYRICA® CR (pregabalin) extended-release tablets, for oral use, CV
Initial U.S. Approval: 2004

INDICATIONS AND USAGE

LYRICA CR is indicated for the management of:

- Neuropathic pain associated with diabetic peripheral neuropathy (DPN) (1)
- Postherpetic neuralgia (PHN) (1)

Efficacy of LYRICA CR has not been established for the management of fibromyalgia or as adjunctive therapy for adult patients with partial onset seizures.

DOSAGE AND ADMINISTRATION

- LYRICA CR should be administered once daily after an evening meal. It should be swallowed whole and should not be split, crushed, or chewed. (2.1)
- Dosing recommendations for LYRICA CR:

Indication	Dosing Regimen	Initial Dose	Maximum Dose
DPN Pain (2.2)	Single dose per day	165 mg/day	330 mg/day within 1 week.
PHN (2.3)	Single dose per day	165 mg/day	330 mg/day within 1 week. Maximum dose of 660 mg/day.

- Conversion from LYRICA Capsules or Oral Solution to LYRICA CR: See full prescribing information. (2.4)
- Dose modification recommended in patients with renal impairment.

WARNINGS AND PRECAUTIONS

- Angioedema: Angioedema (e.g., swelling of the face, mouth (tongue, lips, and gums) and neck (throat and larynx)) can occur and may be associated with life-threatening respiratory compromise requiring emergency treatment. Discontinue LYRICA CR immediately in patients with these symptoms. (5.1)
- Hypersensitivity reactions: Hypersensitivity reactions (e.g., hives, dyspnea, and wheezing) can occur. Discontinue LYRICA CR immediately in these patients. (5.2)
- Suicidal Behavior and Ideation: Antiepileptic drugs, including pregabalin, the active ingredient in LYRICA CR, increase the risk of suicidal thoughts or behavior. (5.3)
- Peripheral Edema: May cause peripheral edema. Monitor patients for the development of edema when co-administering LYRICA CR and thiazolidinedione antidiabetic agents. (5.4)
- Dizziness and Somnolence: May cause dizziness and somnolence and impair patients ability to drive or operate machinery. (5.5)
- Increased seizure frequency may occur in patients with seizure disorders if LYRICA CR is rapidly discontinued. Withdraw LYRICA CR gradually over a minimum of 1 week. (5.7)

ADVERSE REACTIONS

Most common adverse reactions reported in greater than or equal to 4% of patients treated with LYRICA CR are dizziness, somnolence, headache, fatigue, peripheral edema, nausea, blurred vision, dry mouth, and weight gain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at (800) 438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. Advise of potential risk to the fetus. (8.1)

FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR)

When used with CNS depressants or in patients with lung problems

- OTHER BOXED WARNINGS FOR MANY OF THESE AGENTS INCLUDE SERIOUS DERMATOLOGIC REACTIONS, APLASTIC ANEMIA, AND AGRANULOCYTOSIS WITH CARBAMAZEPINE AND HEPATOTOXICITY, FETAL RISK, AND PANCREATITIS WITH DIVALPROEX SODIUM/VALPROATE SODIUM.

On December 19, 2019 FDA is warning that serious breathing difficulties with use of Gabapentin and pregabalin: including with the use of opioid pain medicines and other drugs that depress the central nervous system (or CNS), and conditions such as chronic obstructive pulmonary disease that reduce lung function. **The elderly are also at higher risk.**

Gabapentinoid medicines are associated with misuse and abuse. Gabapentinoids are often combined with Opioids, Muscle Relaxants , BZD's, and other CNS depressants, which increases the risk of respiratory depression. There is less evidence supporting the risk of serious breathing difficulties in healthy individuals taking gabapentinoids alone.

CLINICAL PEARLS- *PULSE OX EVALUATIONS AT EACH APPT?*

Adverse Effects of 2nd Generation AEDs

Adverse Effect	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate	Zonisamide
Dizziness/ataxia	3	3	3	2	2
Somnolence	3	1	3	3	3
Fatigue	2	1	2	1	1
Cognitive dysfunction	1	1	1	3	1
Diplopia	1	3	3	1	1
Nausea/vomiting	1	3	3	1	1
Anorexia/weight loss	0	0	0	3	3
Kidney stones	0	0	0	1	1
Rash	0	3†	0	0	1‡

*The grading system used in this table is as follows: 0 = same as placebo; 1 = 2%–5% more than placebo; 2 = 6%–10% more than placebo or >2 times placebo; 3 = >10% more than placebo or >3 times placebo.

†<1% Incidence of serious rash.

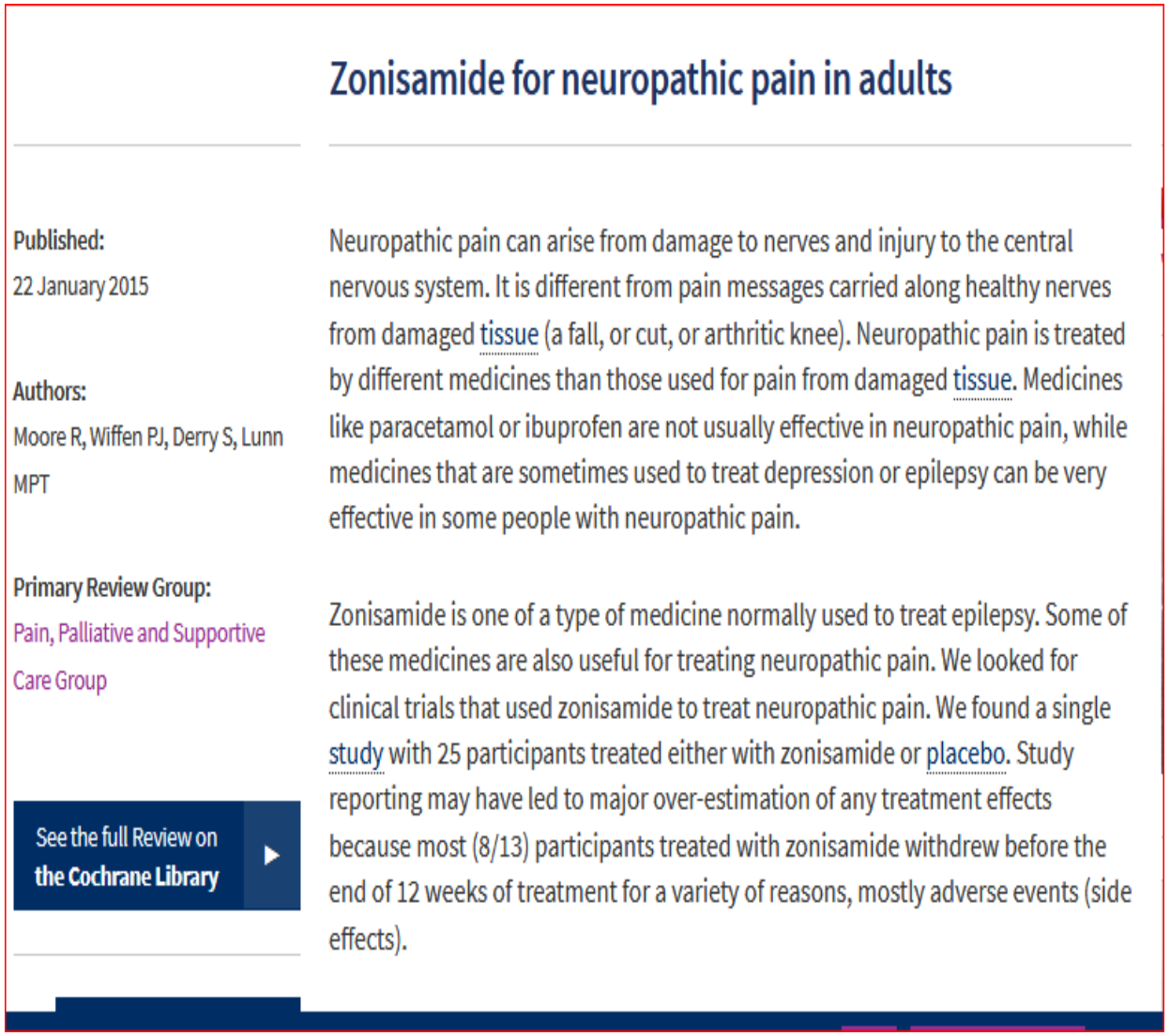
‡<0.1% Incidence of serious rash.

Pappagallo et al. *Clinical Therapeutics* 2003

Anticonvulsants exhibit a wide range of potential adverse effects including sedation, weight gain/loss, renal stones, edema, forgetfulness, word-finding difficulty, teratogenicity, and sometimes poor balance.

Stevens–Johnson syndrome/toxic epidermal necrolysis *Rashes* occur in up to 2% of patients treated with *zonisamide* (*Zonegran*) and may be more common in patients receiving *zonisamide* in combination with first-generation AEDs.

www.ncbi.nlm.nih.gov › pmc › articles › PMC5799627



Zonisamide for neuropathic pain in adults

Published:
22 January 2015

Authors:
Moore R, Wiffen PJ, Derry S, Lunn MPT

Primary Review Group:
Pain, Palliative and Supportive Care Group

See the full Review on the Cochrane Library

Neuropathic pain can arise from damage to nerves and injury to the central nervous system. It is different from pain messages carried along healthy nerves from damaged tissue (a fall, or cut, or arthritic knee). Neuropathic pain is treated by different medicines than those used for pain from damaged tissue. Medicines like paracetamol or ibuprofen are not usually effective in neuropathic pain, while medicines that are sometimes used to treat depression or epilepsy can be very effective in some people with neuropathic pain.

Zonisamide is one of a type of medicine normally used to treat epilepsy. Some of these medicines are also useful for treating neuropathic pain. We looked for clinical trials that used zonisamide to treat neuropathic pain. We found a single study with 25 participants treated either with zonisamide or placebo. Study reporting may have led to major over-estimation of any treatment effects because most (8/13) participants treated with zonisamide withdrew before the end of 12 weeks of treatment for a variety of reasons, mostly adverse events (side effects).

Carisoprodol is a prescription drug marketed since 1959. It is a centrally acting muscle relaxant. The diversion and abuse of carisoprodol increased in the last have decade.

Elimination half-life of approximately 2 hours after administration of a single dose of 350 mg of carisoprodol. The half-life of meprobamate is approximately 10 hours after administration of a single dose of 350 mg of carisoprodol.

On December 12, 2011, DEA published a Final Rule (76 FR 77330) in the Federal Register: making The Final Rule states that effective January 11, 2012, all prescriptions for drugs containing carisoprodol =schedule IV controlled substance.

Generic Name	Brand Name
Skeletal Muscle Relaxants[1]	
Carisoprodol	Soma
Chlorzoxazone	Parafon Forte DSC
Cyclobenzaprine	Flexeril
Methocarbamol	Robaxin
Orphenadrine	Norflex
Tizanidine	Zanaflex

Baclofen is another **muscle relaxer.** (Lioresal) Oral Tabs: 5mg, 10mg, 20mg = Abrupt discontinuation of **baclofen** may cause **seizures**

- *EASY TO START…HARD TO GET PATIENTS OFF…ARE THEY REALLY BEING USED FOR SPASMS OR AS HYPNOTICS/SEDATIVES? PRN USE-*

The recommended maximum duration of SOMA use is up to two or three weeks. The recommended dose of **SOMA** is 250 mg to 350 mg three times a day and at bedtime. The recommended maximum **duration** of **SOMA** use is up to 2-3weeks.

Controlled substance combo's= Most pharmacies will not fill BZD+SOMA+ OPIOID= "Trinity" HOLY TRINITY- DO NOT PRESCRIBE COMBINATION!

- **Amitriptyline and venlafaxine** are probably effective in migraine prevention

- Amitriptyline, duloxetine, and milnacipran in the management of fibromyalgia

- Duloxetine conditionally recommended for patients with knee, hip, and/or hand OA

Clinicians should also be aware of more common adverse effects of the adjuvant agents. The anticholinergic effects of the TCAs (eg, dry mouth, blurred vision, urinary retention, constipation) are well known and undesirable; however, the sedative and antidepressant properties of these agents may be beneficial in patients with chronic pain experiencing anxiety and/or depression.

The TCAs and SNRIs have a boxed warning regarding an increased risk of suicidal thinking and behavior in children, adolescents, and young adults. Patients of any age who initiate antidepressant therapy should be closely monitored for clinical worsening. The most commonly occurring adverse effects with the SNRIs include nausea, dry mouth, dizziness, headache, and excessive sweating.

Duloxetine (Cymbalta) approved for the treatment of depression and diabetic peripheral neuropathy (DPN)

-Used to treat depression, anxiety, fibromyalgia, and diabetic neuropathy & to treat chronic musculoskeletal *pain*, including *pain* caused by osteoarthritis and chronic low back *pain*

-FDA Approves Cymbalta for Chronic Musculoskeletal Pain (Nov 5, 2010)
The approved dose for chronic musculoskeletal pain is a 60-milligram capsule taken once a day. DO NOT USE WITH PATIENTS WITH LIVER ISSUES!

- *TCA'S ARE STILL OPTIONS!*

Buprenorphine Products for treatment of opioid use disorder (OUD) & Pain

Sublingual Tablets and Film Strips-The film strips =dissolve fast and less bitter taste. The naloxone is included to prevent drug abusers from crushing the tab or strip and inhaling it or dissolving and injecting the medication.
Naloxone has a very poor sublingual (SL) and oral bioavailability (less than 2 percent). However, naloxone has a very high intranasal and IV bioavailability, which is a deterrent to misuse of the medication. When Suboxone is taken sublingually as intended, the naloxone has no bioavailability and no effect.

Effective intrathecally for pain states (e.g. phantom limb pain), transdermal, etc.

SUBUTEX IS ONLY PRODUCED IN TABLET FORM.

AVAILABLE IN 2 MG AND 8 MG STRENGTHS.(WITHOUT NALOXONE) THE TABLET SHOULD BE PLACED UNDER THE TONGUE AND ALLOWED TO FULLY DISSOLVE, AS SWALLOWING WILL REDUCE BIOAVAILABILITY AND IS NOT RECOMMENDED.

HTTPS://WWW.ACEPNOW.COM/ARTICLE/A-QUICK-GUIDE-TO-BUPRENORPHINE-PRODUCTS/

The half-life of buprenorphine is approximately 37 HOURS, depending on the mode of administration.
The elimination half-life is more difficult to estimate =The drug's pain-relieving properties last on average 6 to 8 hours when given PO.

- BUPRENORPHINE WAS DEVELOPED BY UK-BASED RECKITT & COLMAN PRODUCTS AND RELEASED IN ENGLAND IN 1978. THAT SAME YEAR, A CLINICAL STUDY DETERMINED THAT BUPRENORPHINE COULD BE HELPFUL IN **REDUCING CRAVINGS OF PURE OPIOIDS IN PATIENTS WITH AN OPIOID ABUSE DISORDER.** THEN, A SEPARATE STUDY PUBLISHED IN 1982 DEMONSTRATED THAT BUPRENORPHINE OFFERED EXCELLENT ANALGESIA WITH A BLUNTED ABUSE LIABILITY

Buprenorphine is a partial agonist at the mu-opioid receptors and an antagonist at the kappa receptors. Mu-opioid receptor activity produces the analgesic effects of buprenorphine, while a strong affinity for the kappa receptors render them inactive.

Because of this unique pharmacology, buprenorphine provides analgesia at therapeutic doses but also has a suggested “ceiling effect” on respiratory depression. As the dosage increases, activity that buprenorphine exhibits as a partial agonist plateaus regardless of subsequent increases.
Because of its “ceiling effect” at the opioid receptor, buprenorphine has a much lower likelihood of respiratory depression. QT PROLONGATION!!

HTTPS://WWW.PHARMACYTIMES.COM/CONTRIBUTOR/JEFFREY-FUDIN/2016/03/A-BRIEF-REVIEW-OF-BUPRENORPHINE-PRODUCTS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue buprenorphine and naloxone sublingual film if serotonin syndrome is suspected. (7)

Table 1: Available Doses of Buprenorphine/Naloxone Combination Products*

Suboxone SL Tablet	Suboxone SL Film	Zubzolv SL Tablet	Bunavail Buccal Film
2 mg / 0.5 mg	2 mg / 0.5 mg	1.4 mg / 0.36 mg	----------
4 mg / 1 mg	4 mg / 1 mg	----------	2.1 mg / 0.3 mg
8 mg / 2 mg	8 mg / 2 mg	5.7 mg / 1.4 mg	4.2 mg / 0.7 mg
12 mg / 3 mg	8 / 2 mg + TWO 2 mg / 0.5 mg films	----------	6.3 mg / 1 mg

*(buprenorphine dose/naloxone dose)

12MG SUBOXONE FILM IS ALSO AVAILABLE

Drug Alcohol Depend. 2007 Oct 8; 90(2-3): 261–269.
Published online 2007 May 22. doi: 10.1016/j.drugalcdep.2007.04.006
PMCID: PMC2094723
NIHMSID: NIHMS30198
PMID: 17517480 **Results:**

Six subjects did not complete the study. Of the ten who completed, **three tolerated up to 32/8 mg of buprenorphine/naloxone without evidence of precipitated withdrawal.** For the seven completing both phases, split doses generally produced less precipitated withdrawal compared to full doses.

Conclusions

There is considerable between subject variability in sensitivity to buprenorphine's antagonist effects. Low, repeated doses of buprenorphine/naloxone (e.g., 2/0.5 mg) may be an effective mechanism for safely dosing this medication in persons with higher levels of physical dependence.

Sublingual Buprenorphine/Naloxone Precipitated Withdrawal in Subjects Maintained on 100 mg of Daily Methadone

The findings suggest that partial agonist-related precipitated withdrawal is not an inevitable outcome for persons with high levels of physical dependence, and that the bolus of drug administration is an important variable in its production. The administration of repeated, small doses of buprenorphine/naloxone may be the optimal mechanism for transitioning patients with higher levels of opioid physical dependence onto sublingual buprenorphine/naloxone.

SOME PRESCRIBERS HAVE FEAR OF BUPRENORPHINE-PRECIPITATED WITHDRAWAL,

Table II: Brand Preparations of Buprenorphine Currently Approved in the US.

Type	Buprenorphine	Buprenorphine/Naloxone	Buprenorphine long-acting
Indication	pain	opioid dependence substitution indication	opioid dependence substitution indication
Brands (available doses)	Belbuca (75, 150, 300, 450, 600, 750, or 900 mcg)	Suboxone (2/0.5, 4/1, 8/2, or 12/3 mg)	Sublocade injection (100, 300 mg monthly)
	Butrans (5, 7.5, 10, 15, or 20 mcg/h or a 7-day patch)	Zubsolv (0.7/0.18, 1.4/036, 2.9/071, 5.7/1.4, 8.6/2.1, 11.4/2.9 mg)	Probuphine implant (74.2 mg every six months)
	Buprenex (300 mcg/ml via intramuscular or intravenous administration)	Bunavail (2.1/0.3, 4.2/0.7, 6.3/1 mg)	Brixadi injection (8, 16, 24 or 32 mg weekly; 64, 96, or 128 mg monthly)

*Information based on corresponding package inserts.

Belbuca: buccal formulation of buprenorphine approved by the FDA for the treatment of pain.

Belbuca can be delivered by dissolving a film that is placed on the inner lining of the cheek for the treatment of chronic pain

BRIXADI™ *is a long-acting buprenorphine injectable* ***with both weekly and monthly doses*** *to align with the way healthcare providers treat patients with OUD*

Plymouth Meeting, Pa. — December 23, 2018 — Braeburn today announced that the U.S. Food and Drug Administration (FDA) has granted tentative approval of BRIXADI (buprenorphine) extended-release weekly (8mg, 16mg, 24mg, 32mg) and monthly (64 mg, 96mg, 128mg) injections. The tentative approval is for use of BRIXADI for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.

https://braeburnrx.com/braeburn-announces-tentative-fda-approval-of-brixadi-buprenorphine-extended-release-injection-for-the-treatment-of-moderate-to-severe-opioid-use-disorder/

Never marketed???

BUTRANS=A transdermal buprenorphine patch

CAUTION WITH ADDITIONAL AGENTS WITH POTENTIAL FOR QT PROLONGATION - METHADONE,AMIODARONE, FLUOROQUINOLONE ANTIBIOTICS, TRICYCLIC ANTIDEPRESSANTS (TCAS), SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS), AND ATYPICAL ANTIPSYCHOTICS. SEROTONIN SYNDROME RISK!!!

QT PROLONGATION WITH SSRIS VERSUS PLACEBO AND SSRIS VERSUS TCAS, SSRIS WERE ASSOCIATED WITH A 6.10 MS QTC INCREASE. TCAS WERE ASSOCIATED WITH AN ADDITIONAL 7.05 MS QTC INCREASE COMPARED WITH SSRIS. OF NOTE, CITALOPRAM AND ESCITALOPRAM WERE THE SSRIS WITH THE MOST NOTABLE QT PROLONGATION, WITH QTC CHANGE VERSUS PLACEBO OF +10.58MS AND +7.27MS, RESPECTIVELY.

BUTRANS PATCH: Approved for pain management = 5, 7.5, 10, 15, and 20 mcg/h doses, delivered over 7 days.

Lower doses compared to those available across the European Union (EU)?

FDA had concerns regarding QT interval prolongation that occurred in several patients during US-based clinical trials. In the US, the buprenorphine patch is FDA indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time.

It is recommended to discontinue around-the-clock opioids prior to initiating buprenorphine: Short-acting opioids may be used during titration periods. May want to consider taper for patients first if on >30mg MEDD to 30 mg MEDD prior to initiation.

- A CLINICAL STUDY IN 1988 DEMONSTRATED THAT NALOXONE REVERSAL OF BUPRENORPHINE FAILED TO PRECIPITATE ABSTINENCE AND ABRUPT WITHDRAWAL IN ANIMALS AND HUMANS, PRODUCING ONLY MILD WITHDRAWAL EFFECTS.

Buprenorphine-containing options:

sublingual buprenorphine tabs,
sublingual buprenorphine/naloxone tabs/film,
buccal buprenorphine,
transdermal buprenorphine (patch)

Buprenorphine (Belbuca): buccal film
Start with a low dose to establish tolerability- **Consider the dosing schedule based on morphine sulfate equivalents (MSE) listed below:**
Belbuca
Belbuca is indicated for the management of pain requiring around-the-clock, long-term opioid treatment not adequately controlled with alternatives. This reflects the new standard labeling required of all extended-release opioids indicated for chronic pain.

FOR PATIENTS TAKING LESS THAN 30 MG ORAL MSE, INITIATE THERAPY WITH 75 MCG ONCE DAILY OR EVERY 12 HOURS. FOR PATIENTS TAKING BETWEEN 30 MG AND 89 MG ORAL MSE, INITIATE THERAPY WITH 150 MCG BELBUCA EVERY 12 HOURS FOLLOWING ANALGESIC TAPER. FOR PATIENTS TAKING BETWEEN 90 MG AND 160 MG ORAL MSE, INITIATE THERAPY WITH 300 MCG BELBUCA EVERY 12 HOURS FOLLOWING ANALGESIC TAPER. FOR PATIENTS TAKING GREATER THAN 160 MG ORAL MSE, CONSIDER ALTERNATE ANALGESIC. •BELBUCA DOSES OF 600 MCG, 750 MCG, AND 900 MCG ARE ONLY FOR USE FOLLOWING TITRATION FROM LOWER DOSES OF BELBUCA.

Make sure your fingers are clean and dry. Tear open the foil package by folding on the dotted line and tearing down at the perforation, or by carefully cutting the package with scissors. Remove the buccal film from the package.

-Wet the inside of your cheek with your tongue or with water.

-Place the film on a dry fingertip with the yellow side facing up.

-Press the yellow side against the inside of your cheek and hold in place for 5 seconds.

-Leave BELBUCA® on the inside of your cheek until fully dissolved, usually within 30 minutes.

- *OPIOID-SPARING BENEFITS OF ADJUVANTS ?*

Buprenorphine (Belbuca): buccal film:
Initiate therapy with 75 mcg BELBUCA once daily or every 12 hours, as tolerated, for at least 4 days before increasing dose to 150 mcg every 12 hours.

Peel, place, and press
BELBUCA® works by sticking to the inside of your cheek and dissolving completely—typically within 30 minutes.
BELBUCA® has a mild peppermint taste.

- *OPIOID-SPARING BENEFITS OF ADJUVANTS ?*

LIDODERM PATCH–

Lidocaine produces pain relief through a reversible nerve conduction blockade WHAT TO DO IF ALLERGIC REACTION= SPRAY ANY STEROID NASAL SPRAY (FLONASE) ON THE SKIN AREA (THE BACK,KNEE,NECK) TO REDUCE ADHESIVE MEDIATED ITCHING,RASH –STILL ALLOWS PATCH TO STICK IF YOU ALLOW SPRAY TO DRY FIRST!

Application site reactions (eg, erythema, pain, pruritus) may occur with transdermal lidocaine

_LIDOCAINE PATCH 5%- RX

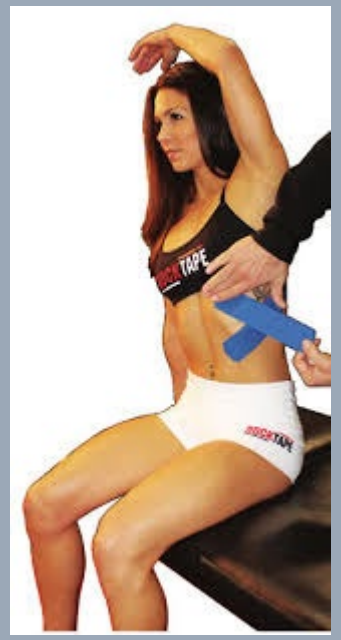
LIDOCAINE PATCH 4%= OTC- *#6 PATCHES FOR UNDER $10.00?*

ZTlido sticks for a FULL 12 HOURS to provide relief from PHN pain

- ZTlido delivers the same amount of pain medication (lidocaine) as conventional lidocaine 5% patches
- But ZTlido has proven to be superior in STAYING ATTACHED versus conventional lidocaine 5% patches - for a FULL 12 HOURS.
- ***Ask yourself: If a patch doesn't stick, does it work?***

- LIDODERM PATCH- A NEW OPTION!
- ZT=_____?

KINESIOLOGY THERAPEUTIC (**KT**) **TAPE** IS USED TO SUPPORT AND RELIEVE **PAIN** IN MUSCLES, JOINTS, AND/OR LIGAMENTS. IT MAY REDUCE SWELLING! MAY BE HELPFUL FOR THOSE WHO SUFFER FROM ARTHRITIS, PINCHED **NERVES**, CARPAL TUNNEL SYNDROME , BACK AND KNEE PAIN, FOR SHOULDER, NECK,BACK PAIN= TRY **TAPING** EITHER SIDE OF THE SPINE



Nerve receptors are located in their skin, as well as in the deep layers of the fascia, muscles, and other connective tissues -> When tape is applied, it causes compression or decompression of these areas, supposedly allowing it to alter pain signals to the brain

Capsaicin depletes & prevents the re-accumulation of substance P (the primary chemical mediator of pain impulses from the periphery to the central nervous system) in peripheral sensory neurons.

Is effective for neuropathic pain states, e.g., Diabetic Peripheral Neuropathy & PHN, also for JOINT PAIN WITH OSTEOARTHRITIS!

QUTENZA® (*capsaicin*) 8% Patch is a prescription medicine used for the management of nerve pain after shingles in adult patients.

A single, 1-hour, localized treatment may provide up to 3 months of relief from post-shingles nerve pain

QUTENZA is a prescription medicine used for the management of nerve pain after shingles in adult patients.

A transient increase in blood pressure has also been noted in patients during and shortly after transdermal capsaicin application

Do not touch the QUTENZA patch with your hands. If you touch the patch, it may cause burning and stinging

SUMMARY

--Clinicians should only consider adjuvants, co-analgesics & Opioids therapy if the benefits on pain and function outweigh the risks to the individual patient. Recommend the combined use of opioid analgesics with nonpharmacologic therapies or nonopioid analgesics if an opioid is not effective alone.

--Nonopioid analgesics are a mainstay of pain control and have a significant role in evidence-based treatment for a variety of conditions

ALAN KAYE and ADAM KAYE POST COVID-19 (NOT A SIDE EFFECT OF JnJ shot?)