PainWeek®

Navigating the Crystal Ball: Drug Development for Acute Pain Management—Phase 1-4 (ACU-01)

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Robert Rafta, PhD

Disclosures

- Keith Candiotti
  - Consultant/Independent Contractor: Baux Bio, Acacia, Takeda, Merck, AcelRx, Pfizer, Pacira, NEMA Research
  - Grant/Research Support: Acacia, Baux Bio, Takeda, AcelRx, Pacira, Pfizer-Grants are to the institution
  - Advisory Board: Takeda, Acacia
- Robert Raffa
  - Consultant/Independent Contractor: Neumentum
  - Stock/Shareholder: Neumentum
- Joseph Pergolizzi
  - Consultant/Independent Contractor: Lilly
  - Grant/Research Support: Regeneron
  - Honoraria: Salix
  - Speaker's Bureau: BDSA
  - Advisory Board: Enalare
  - Stock/Shareholder: Neumentum

Areas of Discussion

- Dr. Bob Raffa – Drug Discovery and Development and Innovation. New agents in early development-Targets and agents.
- Dr. Joseph Pergolizzi – Later development agents. What we will be seeing in the near future?
- Dr. Keith Candiotti – What is new in the US for the treatment of acute pain?

Learning Objectives

- Describe what options for the treatment of acute pain have been recently made available for us in the United States
- Discuss some of the new agents and their indications
- Review limitations of these new drugs

Navigating the Crystal Ball: Drug Development for Acute Pain Management - Phase 1-4 (ACU-01)

- Rate of drug development has decreased over the past decades. In the 1950s @50 drugs per year were introduced. That is now down to about 17/yr since 1965.
- Balance between bringing drugs quickly to market vs protecting the public good
- Modern drugs take a path from pre-clinical studies, to multi-stage trials to post-trial regulatory approval.
- For drugs, full development can take 10-15 years (average 12 years). About 9 out of every 10 new drugs fails once it enters the human testing phase.
- Even at stage III trials, 50% of all drugs still do not make it to market.
- Other industrialized countries have similar issues. In England only 18% of drugs entering phase II trials make it to phase III trials.

Robert B Raffa, PhD

Navigating the Crystal Ball: Drug Development for Acute Pain – *New Targets, New Agents*

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Known Analgesic Targets

- Adenosine
- Alpha$_2$
- Bradykinin
- Cannabinoid
- Capsaicin
- CCK
- CGRP
- Conotoxin
- Endothelin
- Epibatidine
- FMRFamide
- nAChR
- Nav1.*x*
- Neurokinin (SP)
- NPY
- Opioid - peripheral
- P2X
- TRP
- VIP
- ...

Clinical Translation?

- Woolf (2020) Biol Psychia 87:74-81

Table 2. Analgesic Target Clinical Failures

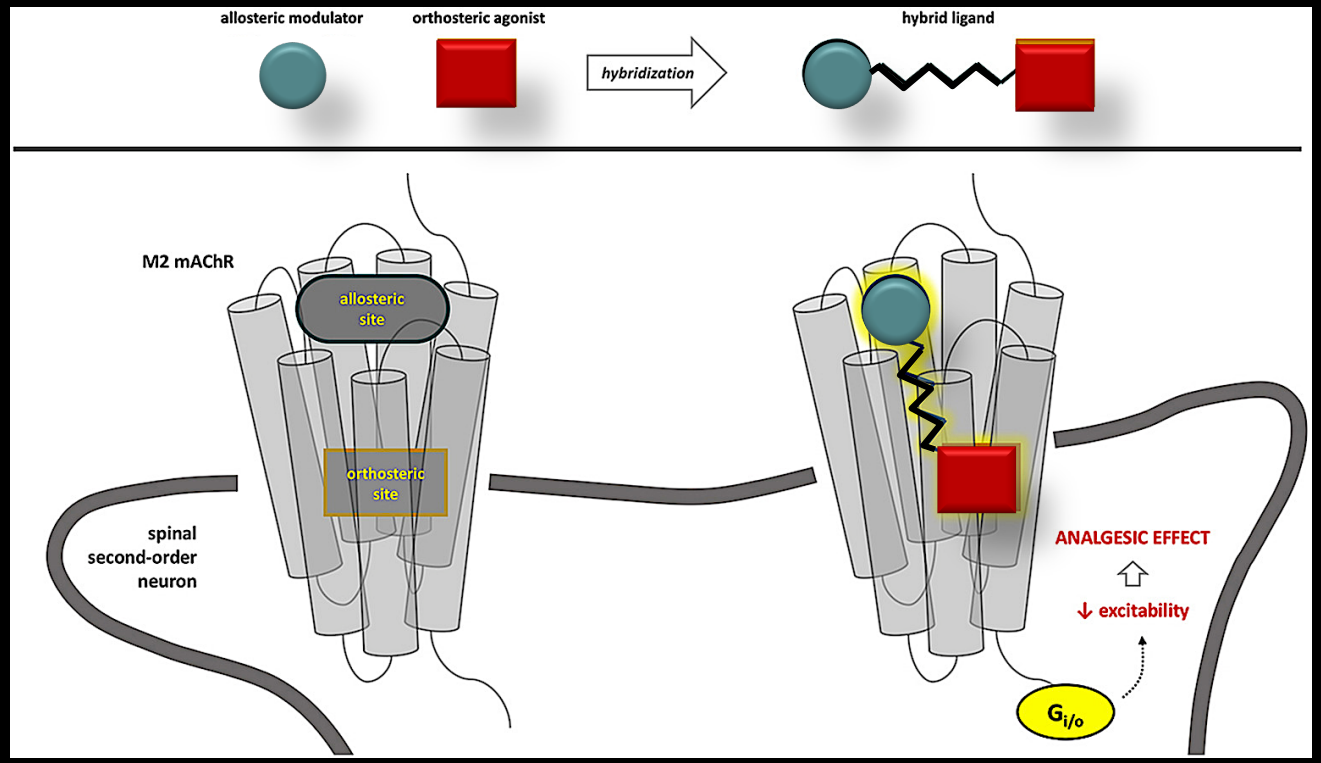
Target	Function of Target
NK1	Substance P/tachykinin receptor antagonist
TRPV1	Noxious heat/proton/capsaicin transducer antagonist
Nav1.7	Voltage-gated sodium channel blocker/nociceptor excitability
Cav3.2	Calcium channel blocker/synaptic transmission
Kv7	Potassium channel opener/nociceptor excitability
FAAH1	Enzyme inhibitor/cannabinoid enhancer
CB1/CB2	Cannabinoid receptors agonists
α2	Adrenergic receptor inhibitor
p38	Intracellular kinase inhibitor
CCR2	Chemokine antagonist

α2, α2 adrenergic receptor; Cav3.2, voltage-gated calcium channel 3.2; CB, cannabinoid receptor; CCR2, C-C chemokine receptor type 2; FAAH1, fatty acid amide hydrolase 1; Kv7, voltage-gated potassium channel 7; Nav1.7, voltage-gated sodium channel 1.7; NK1, neurokinin 1; p38, protein 38; TRPV1, transient receptor potential cation channel subfamily V member 1.

M2 mAChR: hybridization of orthosteric and allosteric ligands

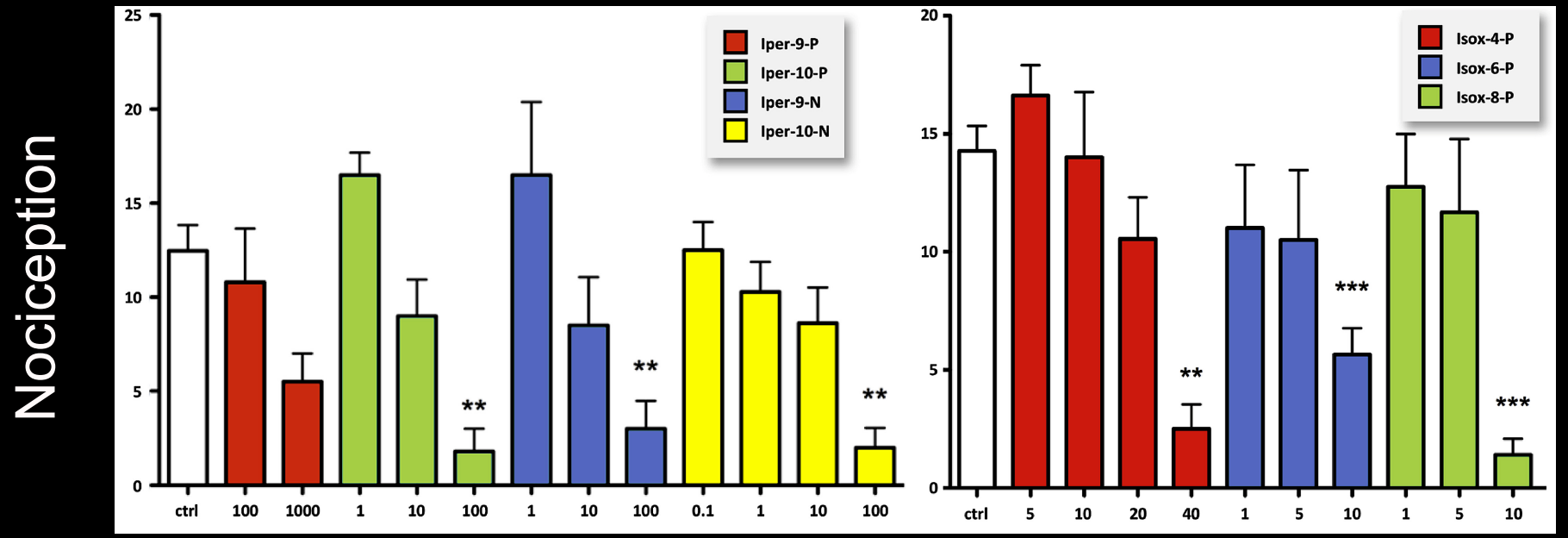
M2 mAChR: hybridization of orthosteric and allosteric ligands

- Matera et al. (2020) Eur J Pharmacol 876:173061



M2 mAChR

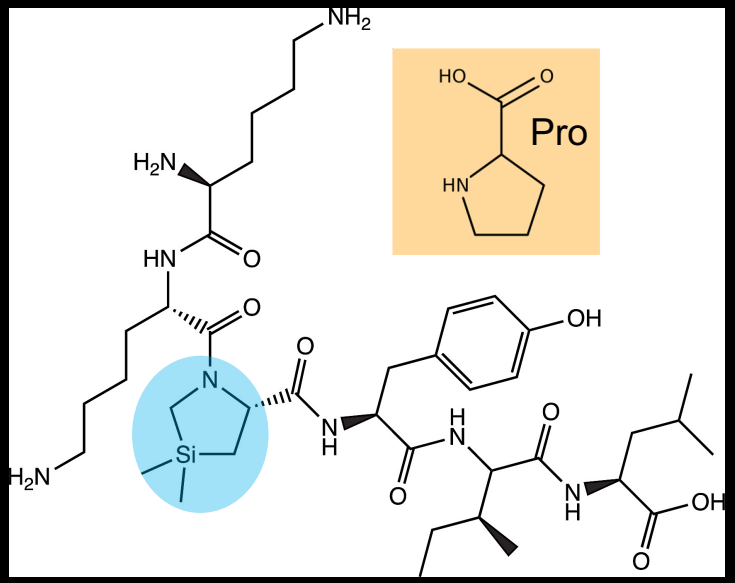
- Acetic-acid (sc) abdominal irritation

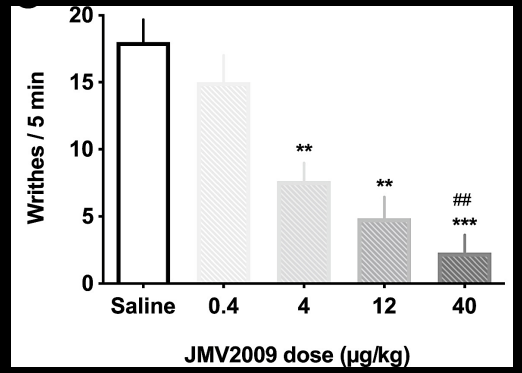


Silylated NT(8-13) Analog

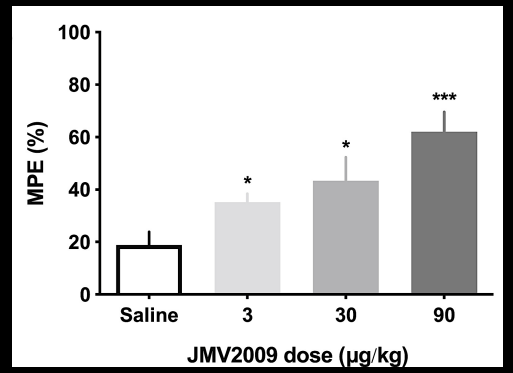
Silylated NT(8-13) Analog

- Tétreault *et al*. (2020) Eur J Pharmacol 882:173174
- Besser-Offroy *et al*. (2020) Data in Brief 31:105884

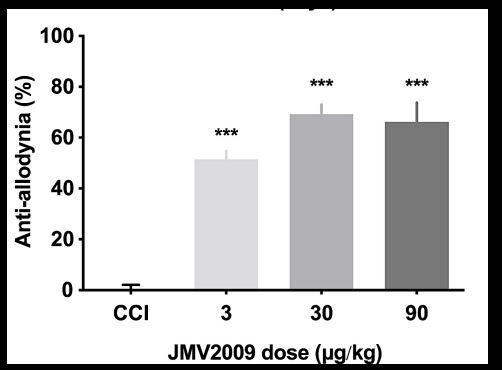




Mo-WR



R-TF

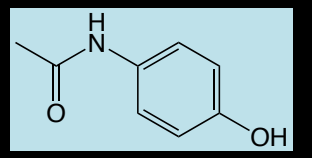


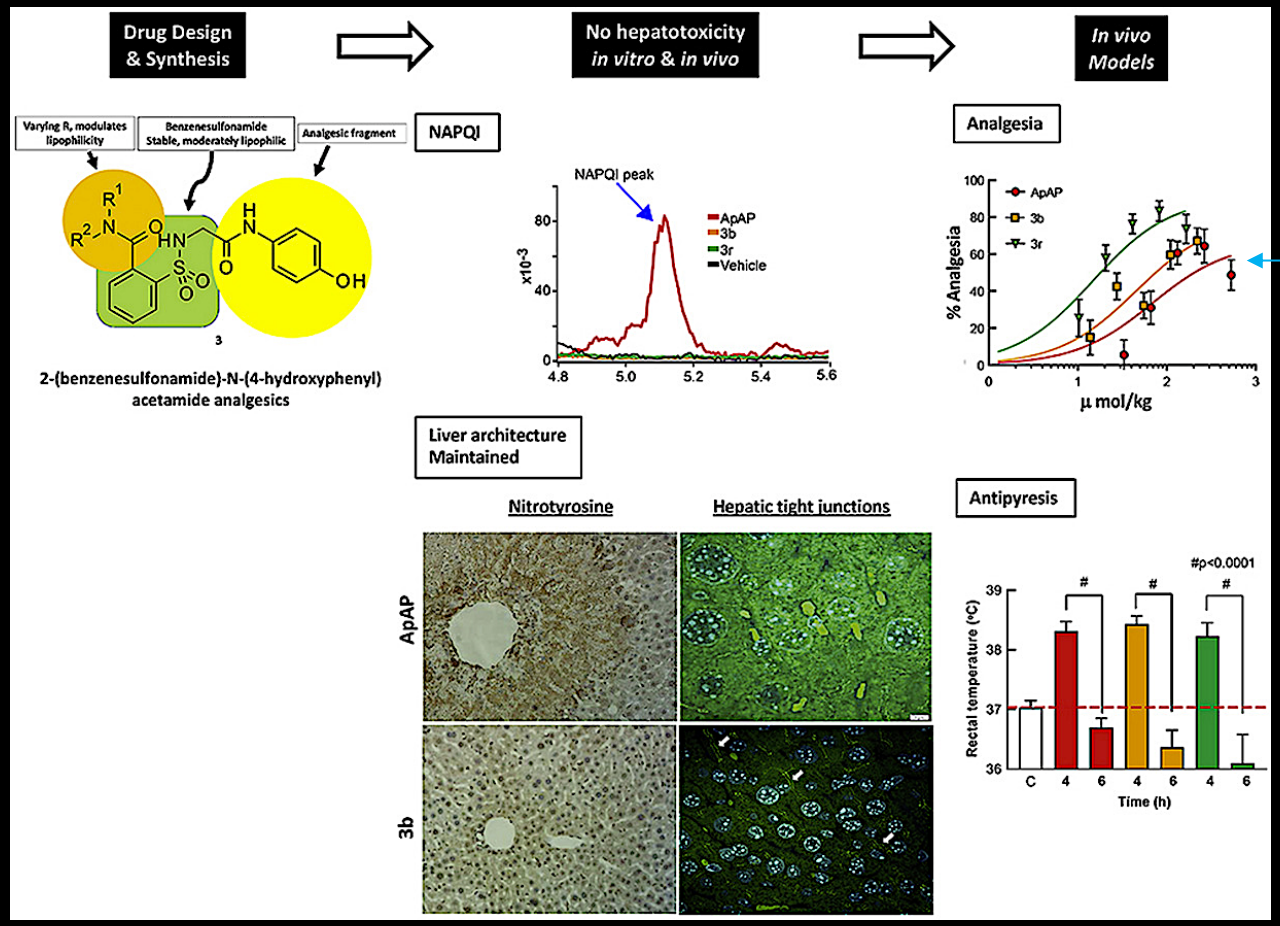
R-MechAllod

APAP Analog: analgesia & antipyresis, lacks hepatotoxicity

APAP Analog

- Bazan et al. (2020) Eur J Med Chem 202: 112600



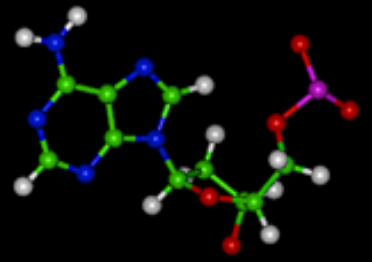


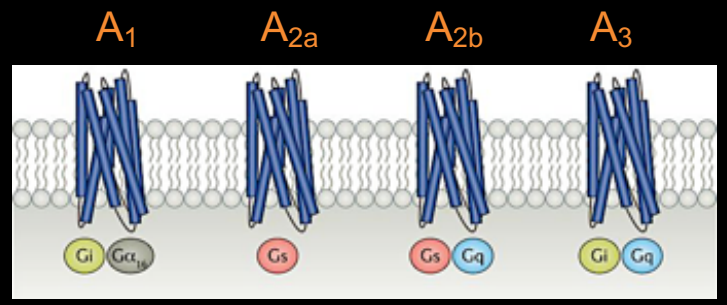
APAP

Chronic Morphine Alters A_3AR Signaling

Adenosine Rreceptors and Analgesia

- Robust antinociception
- Variety of pain types
- Does not alter protective nociception
- Does not produce inherent reward



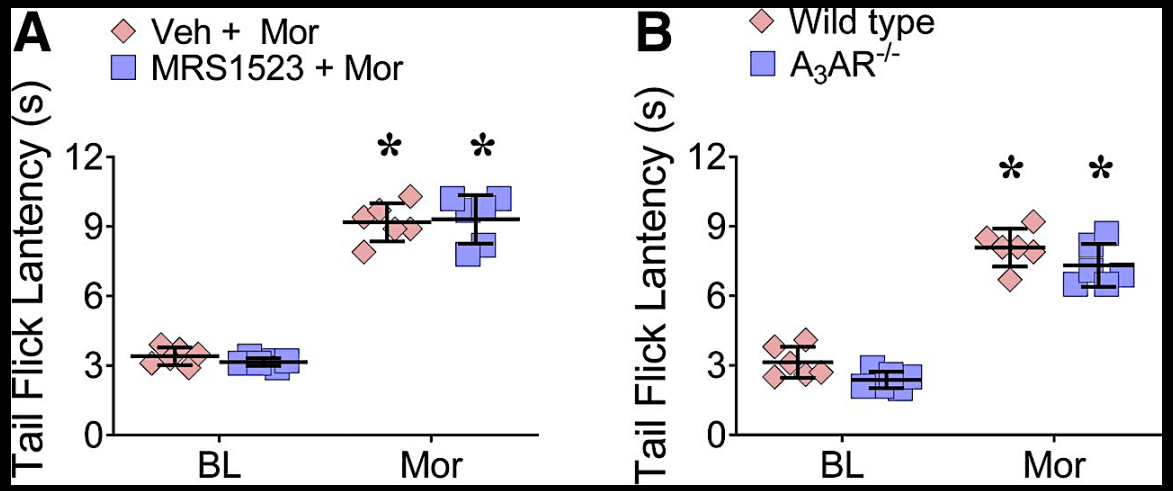


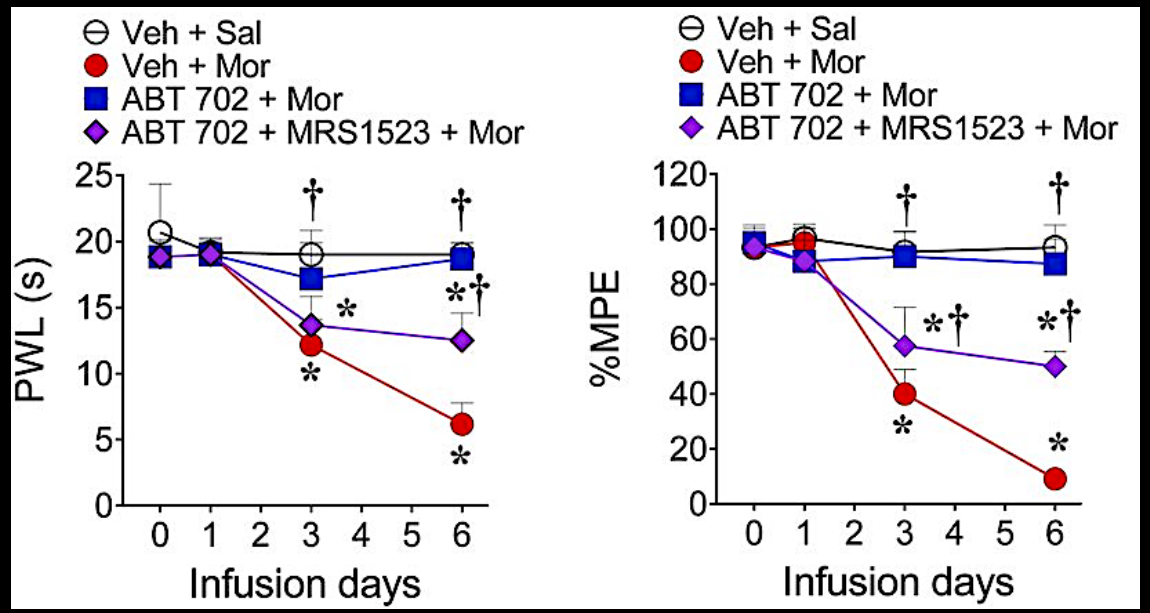
A_1-AR	analgesia	CV AEs
A_{2a}-AR	analgesia	CV AEs
A_{2b}-AR	no analgesia	—
A_3-AR	analgesia	no CV AEs

Borea *et al.* (2018) *The Adenosine Receptors*, Humana Press.

Chronic Morphine Alters A_3AR Signaling

- Doyle et al. (2020) JPET 374:331-341

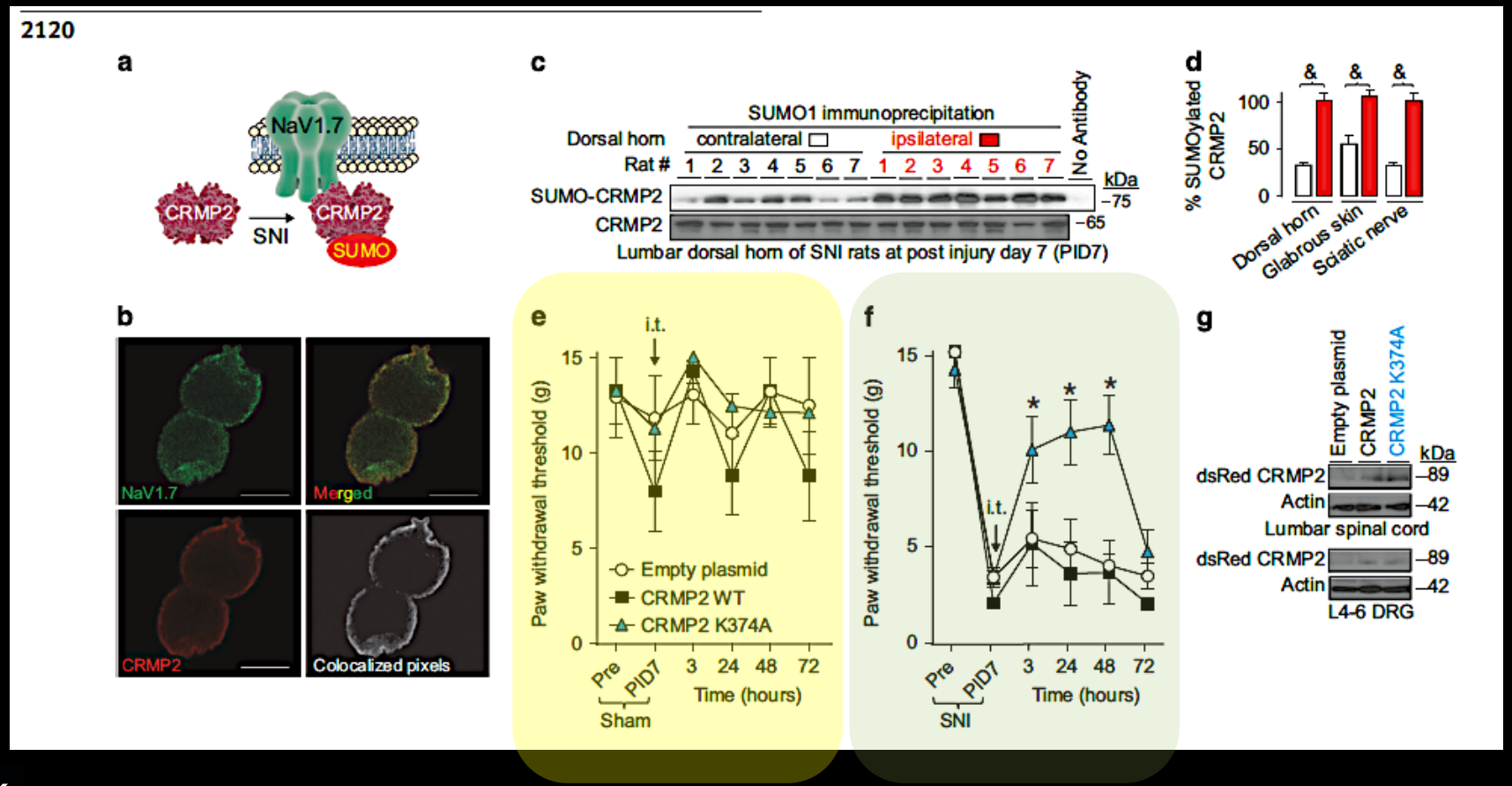




CRMP2 SUMOylation & Neuropathic Pain

CRMP2 SUMOylation & Neuropathic Pain

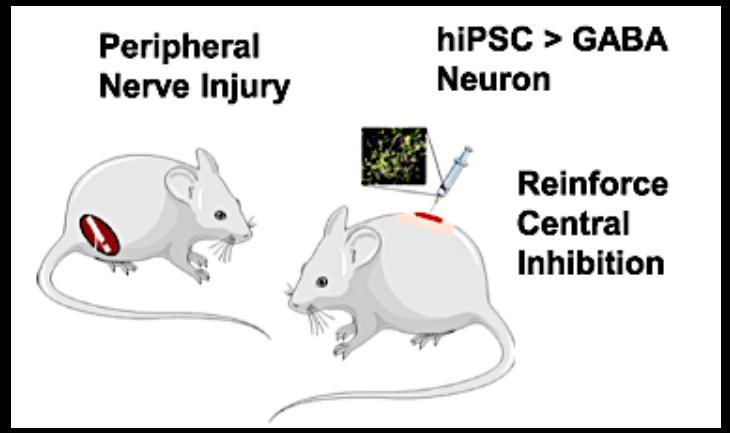
- Moutal *et al*. (2018) Molec Psychia 23:2119-2121

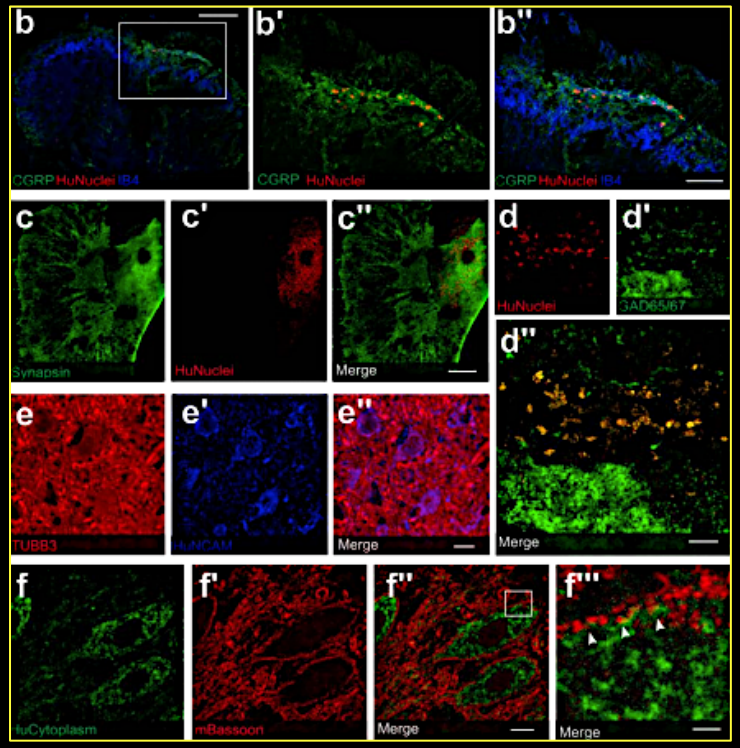


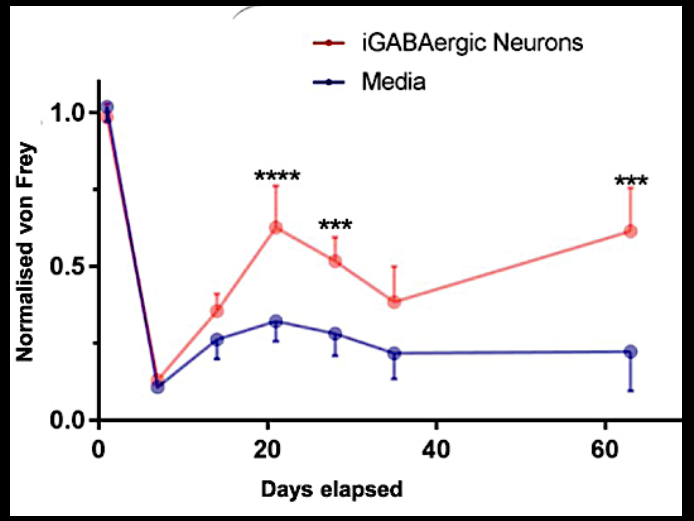
GABAergic Transplants for Neuropathic Pain

GABAergic Transplants for Neuropathic Pain

- Manion et al. (2020) Pain J 161:379-387







Medicinal Chemistry

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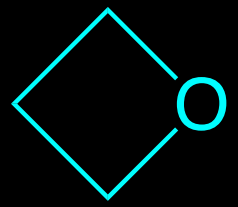
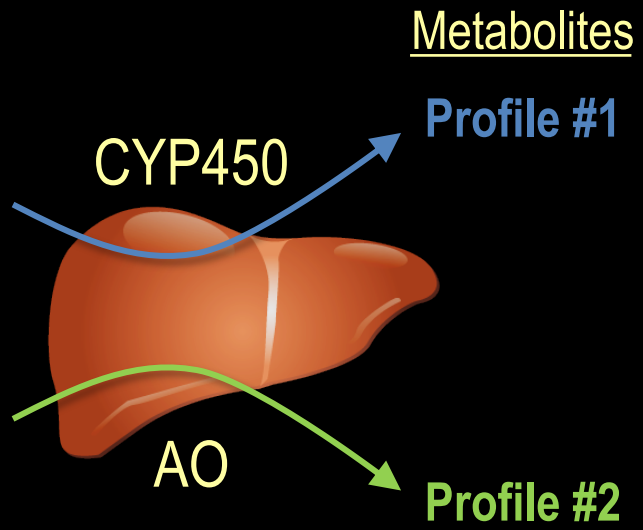
1. Directing Metabolism Away From CYP450

- Reviewed in: Raffa & Pergolizzi (2019) Pharmacol Pharm 10:465-473

CYP2J2	3%	CYP2C8	4.7%
CYP2E1	3%	CYP2B6	7.2%
CYP2D6	20%	CYP2A6	3.4%
CYP2C19	6.8%	CYP1A2	8.9%
CYP2C9	12.8%	CYP3A4/5	30.2%



Oxetane

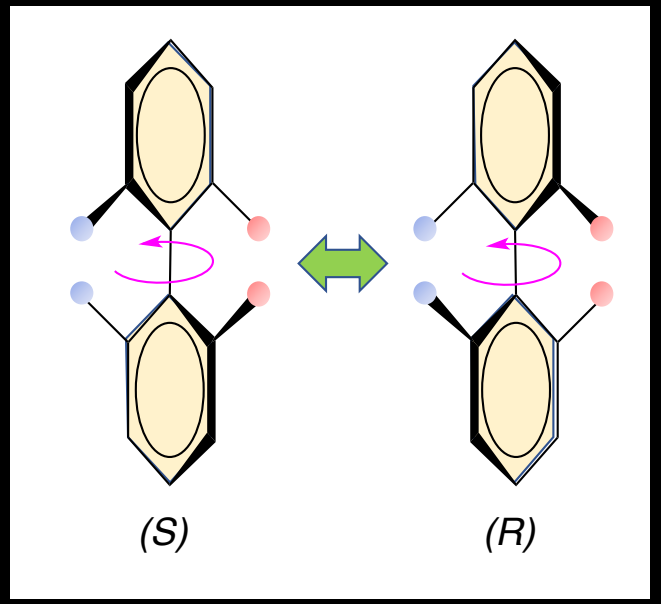


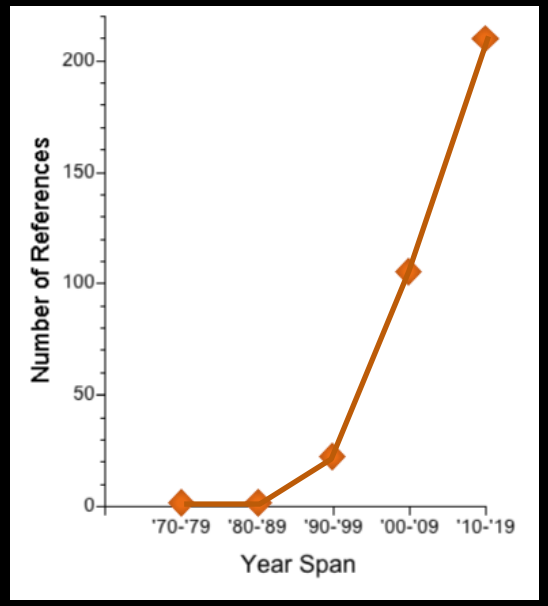
DDIs more likely,
but better understood

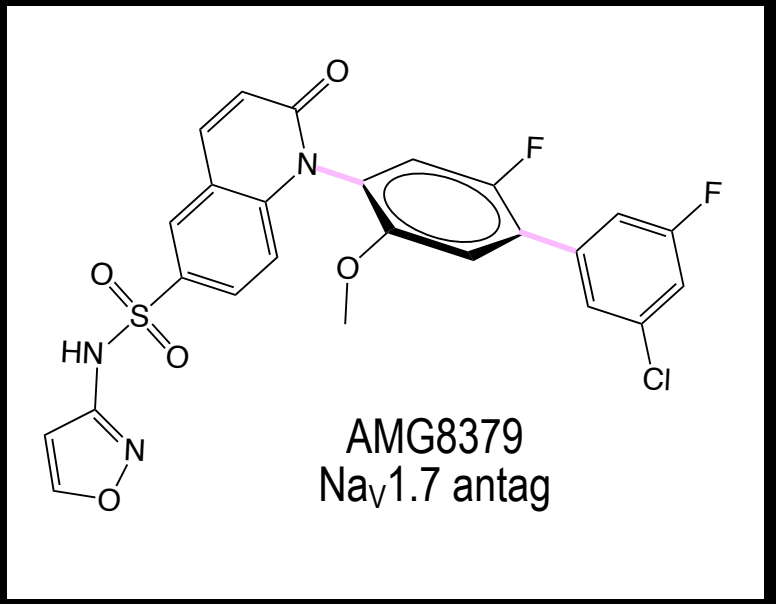
DDIs less likely,
but less understood

2. “Atropisomeric” Drugs: hindered rotation

- Reviewed in: Raffa et al. (2019) Pharmacol Pharm 11:1-8







GPCR Ligands in “Dark Chemical Matter”

GPCR Ligands in Dark Chemical Matter

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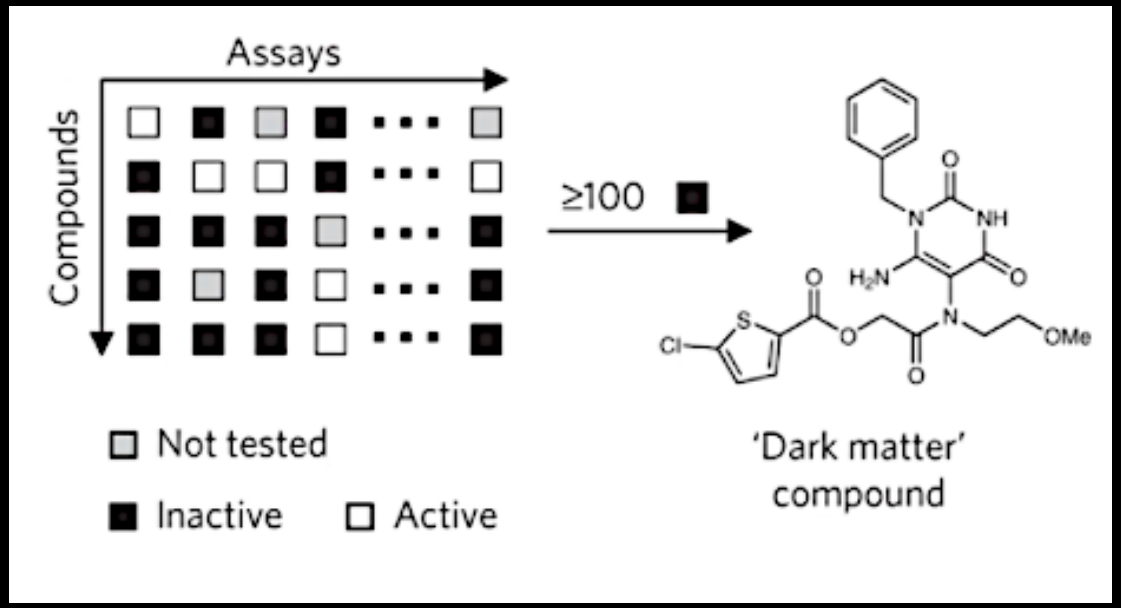
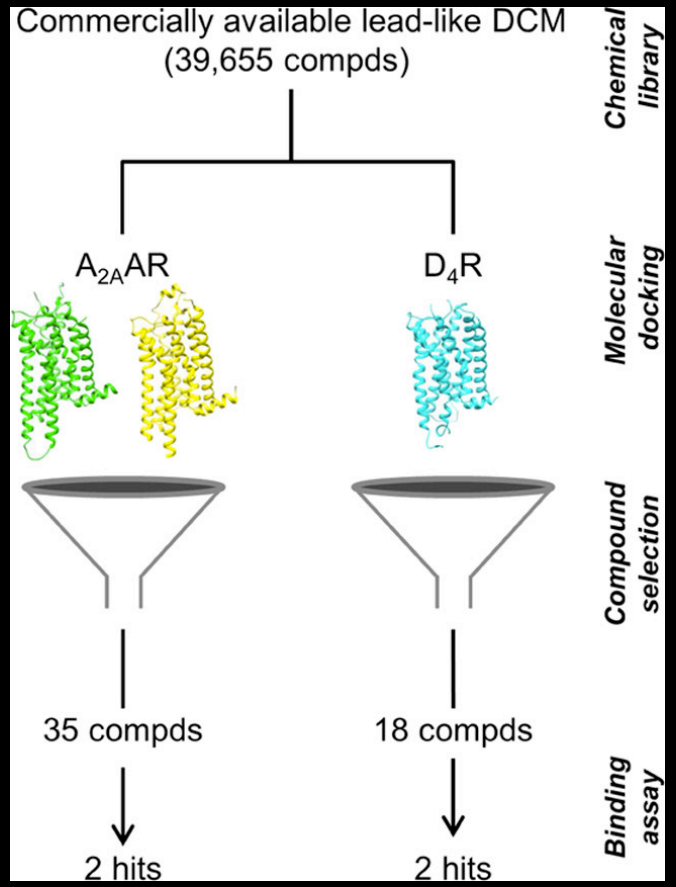
- Ballante et al. (2020) J Med Chem 63:613-620





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- Woolf CJ (2020) Capturing novel non-opioid pain targets. Biol Psychia 87:74-81

Dr. Joseph Pergolizzi

Later development agents.
What we will be seeing in the near future?

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We REALLY Need a Better Mousetrap

PainWeek

Analgesics in Development

- Heron HTX-011received a second complete response letter from the FDA and has filed for a Type A meeting.
- Avenue Therapeutics successfully completed our Phase 3 program of IV tramadol for the management of postoperative pain and we are on track to submit a New Drug Application to the U.S. Food and Drug Administration by year-end.
- Neumentum's Phase I clinical study of a continuously infused NSAID, NTM-001, provided steady plasma levels of ketorolac over 24 hours, with no unexpected adverse effects.
- Nerve growth factors (NGF) is a novel mechanism/target that offers significant potential, but has shown potential safety concerns. Pfizer/Lilly and Regeneron/TEVA programs are running and JNJ ended. (Chronic Pain)

Adapted from OWEN and COMPANY 2019

Heron HTX-011

- A long acting local (LAL) directly into incision sites.
- Claims to be the drug is a biochronomer, a bio-erodible polyorthoester, that allows for a controlled, continuous breakdown to release its drug payload.
- The drug is comprised of the local anesthetic bupivacaine and the NSAID meloxicam in a thick viscous solution that can be delivered without a needle directly into a surgical wound for postoperative pain relief.
- The published literature does not reveal the dosage of each drug within that ratio.
- Concern: There are no data that explore the potential negative side effects of instilling meloxicam directly into the wound. This is particularly important in hip or joint replacement surgeries, where it is essential to prevent infection and promote wound healing to protect the joint.
- Multiple studies suggesting efficacy

Avenue Therapeutics

- IV tramadol 50 mg
- Phase 3 study was to compare the analgesic benefit and tolerability of two doses of IV tramadol (50 mg and 25 mg) to placebo in adult patients undergoing bunionectomy, an orthopedic surgical model.
- Subjects: Bunionectomy (orthopedic surgical mode)
- Results: Established a dose response
  - IV tramadol 50 mg demonstrating a statistically significant benefit ($p<0.05$) over placebo for primary and all key secondary efficacy endpoints,
  - IV tramadol 25 mg demonstrated intermediate results between the 50 mg and placebo arms.
  - IV tramadol 50 mg was well-tolerated.
  - The most common TEAEs were nausea and vomiting.
  - The largest proportion of patients completed IV tramadol 50 mg (98.6%) compared to IV tramadol 25 mg (91.8%) and placebo (88.2%).
- Conclusion: IV tramadol 50 mg was effective and well-tolerated as a treatment for postoperative pain following bunionectomy surgery, while IV tramadol 25 mg, although well-tolerated, was judged to be an ineffective dose for the treatment of pain in this setting.

Neumentum

- A novel, alcohol-free formulation of the powerful NSAID ketorolac, in a pre-mixed bag designed for 24-hours of continuous infusion following surgery.
- Phase I study of NTM-001: Evaluated the pharmacokinetics of NTM-001 continuous infusion compared with ketorolac IV bolus injection every six hours.
- The overall study was comprised of four cohorts with a total of 67 treated subjects across two sites.
- The first study cohort evaluated 24 healthy adults ages 18 to 55 (12 male and 12 female), receiving the full dose of NTM-001 (96.5 mg of ketorolac consisting of a loading dose of 12.5 mg and 3.5 mg/hour continuous infusion over a 24-hour period). The remaining three cohorts evaluated older adults ages 65 or older without and with increasing levels of renal impairment.
- These three cohorts received a dosing regimen that was reduced by 50 percent.
- Conclusion:
  - Phase I results confirm that NTM-001 provides consistent, steady blood plasma levels of ketorolac over 24 hours as predicted by extensive pharmacokinetic and pharmacodynamic modeling that had been previously shared with the US Food and Drug Administration (FDA).
  - Additionally, durable analgesic effect was predicted over 24 hours with a rapid onset anticipated, and NTM-001 was safe and well tolerated.
- This Phase I study is part of a program supporting what has the potential to be the first-ever NSAID approved for continuous infusion.

Nerve Growth Factors (NGF)
Fasinumab

- An antibody to NGF
- Two Phase 3 trials, FACT OA1 and FACT OA2:
  - achieved the co-primary endpoints for fasinumab 1 mg monthly, demonstrating significant improvements in pain and physical function over placebo at week 16 and week 24, respectively.
  - Fasinumab 1 mg monthly also showed nominally significant benefits in physical function in both trials and pain in one trial, when compared to the maximum FDA-approved prescription doses of non-steroidal anti-inflammatory drugs for osteoarthritis.
- The FACT OA1:
  - trial included an additional treatment arm, fasinumab 1 mg every two months, which showed numerical benefit over placebo, but did not reach statistical significance.
- In initial safety analyses from the Phase 3 trials:
  - there was an increase in arthropathies reported with fasinumab. In a sub-group of patients from one Phase 3 long-term safety trial, there was an increase in joint replacement with fasinumab 1 mg monthly treatment during the off-drug follow-up period, although this increase was not seen in the other trials to date. Additional longer-term safety data from the ongoing trials are being collected and are expected to be reported early next year.

Nerve Growth Factors (NGF)

Tanezumab

- An antibody to NGF
- PADUAF Date December 2020
- Trial of 3021
  - Patients with hip or knee OA randomized 1:1:1 to receive either tanezumab, 2.5 mg, every 8 weeks; tanezumab, 5.0 mg, every 8 weeks; or an NSAID daily.
  - These treatments were provided for 56 weeks and the investigators followed up the patients for an additional24 weeks to achieve 80-week follow-up.
  - Tanezumab treated patients did not receive NSAIDs.
- Efficacy:
  - The 5-mg dose of tanezumab was more effective than NSAID for pain relief and functional status improvement.
- Safety:
  - The incidence of the composite adverse joint safety outcome (primarily rapidly progressive OA; also, osteonecrosis and fracture) was 7.1% in the tanezumab, 5mg, group; 3.8% in the tanezumab, 2.5mg, group; and 1.5% in the NSAID group.
  - Similarly, total joint replacement occurred in 8.0% in the tanezumab, 5 mg, group; 5.3% in the tanezumab, 2.5 mg, group; and 2.6% in the NSAID group.

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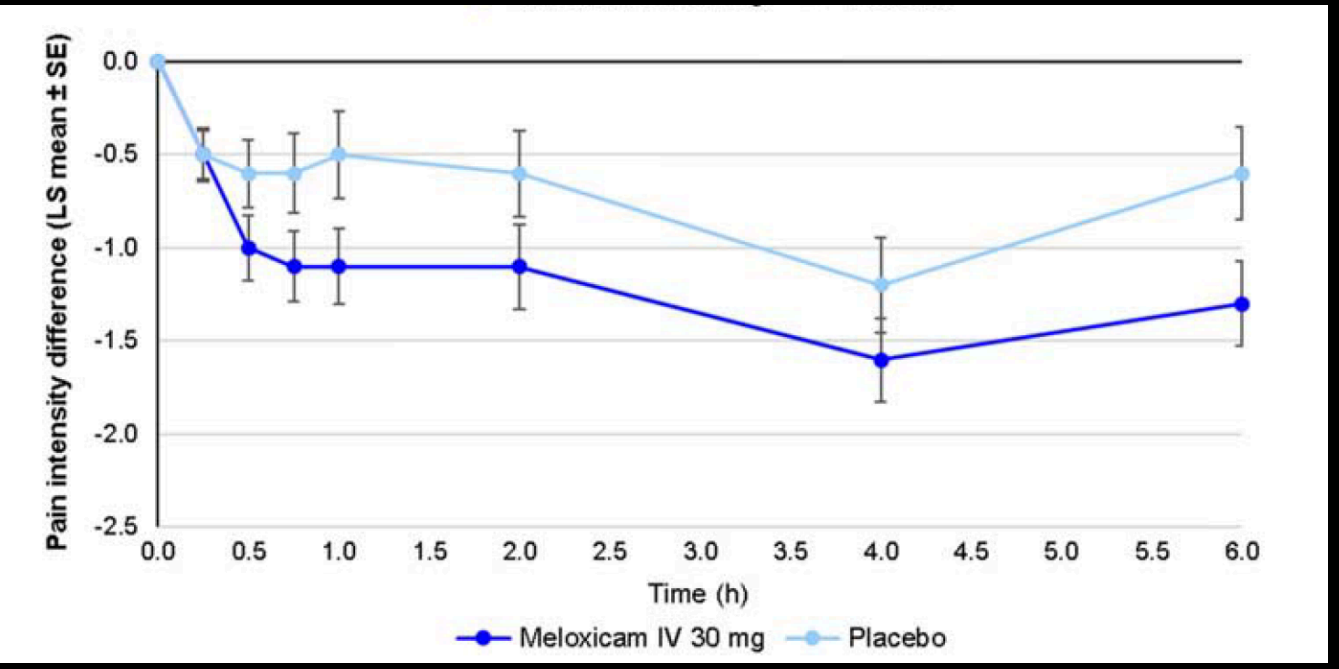
Dr. Keith Candiotti

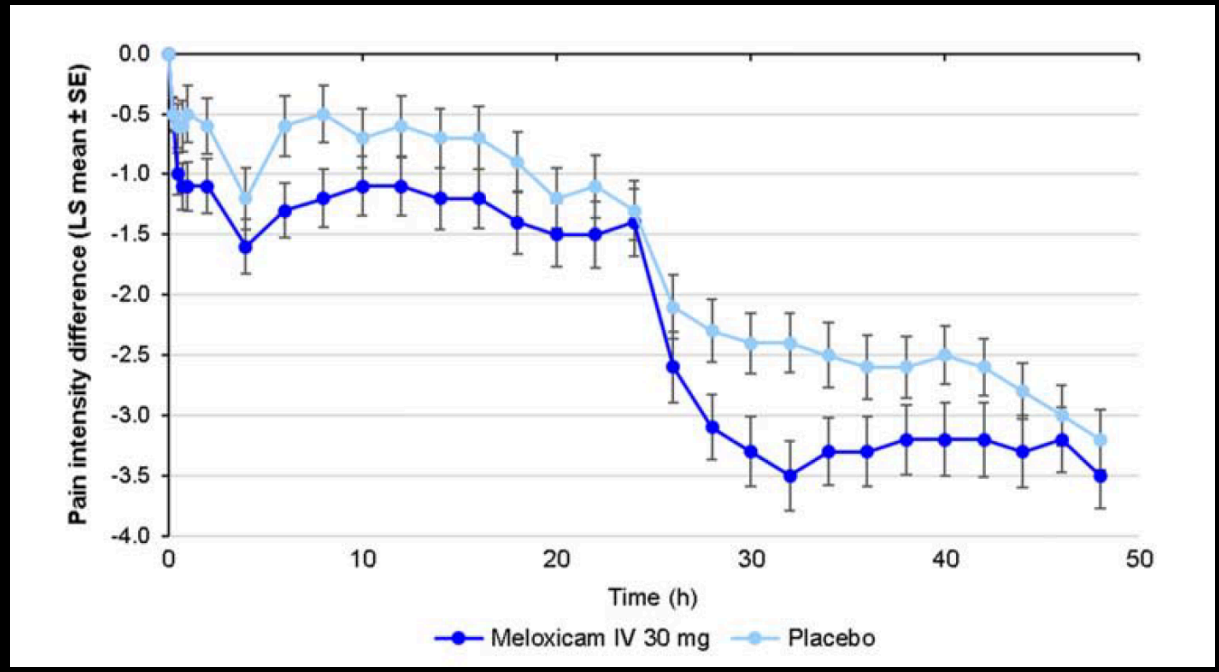
What is new in the US for the treatment of acute pain?

IV Meloxicam

- IV Meloxicam (Anjeso, Baudax Bio) is an IV formulation of the NSAID for once-daily treatment for moderate-to-severe pain in adult.
- While the formulation is unique, this is the same drug as oral meloxicam which has been used for over 20 years.
- COX-2 selective. (Decreases at higher doses).
- Onset is 1-2 hours. Terminal half-life of the IV formulation is around 24 hours.
- Dosing is 30 mg IV over 15 seconds.
- In bunionectomy and abdominoplasty models, pain intensity difference (PID) was significantly better than placebo over 48 hours and 24 hours respectively.
- The effect tapered in the last 6 hours.

Meloxicam

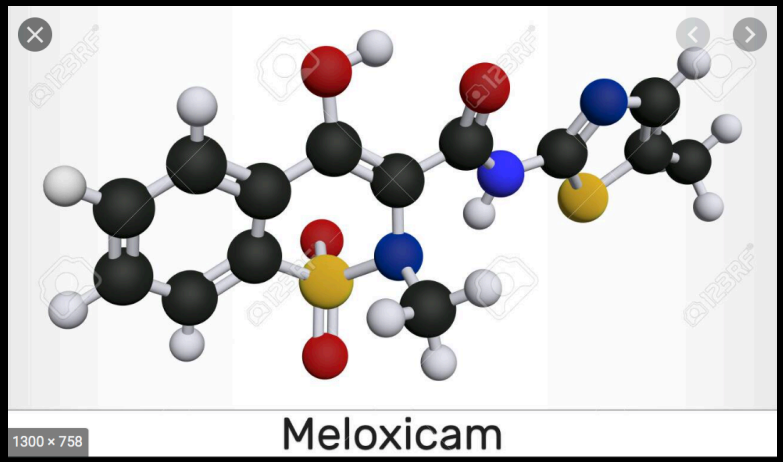




Bunionectomy study, 2018; Meloxicam 30 mg, q24h

IV Meloxicam

- Most patients still required some opioid rescue therapy in the first 24 hours.
- Median time to first rescue was 1-2 hours.
- Median time to meaningful pain relief was 2-3 hours.
- Patients receiving Meloxicam required few opioids in the 48 hours following surgery.
- Meloxicam adverse effects are similar to other NSAID in general. In general Meloxicam was well tolerated and SAE were similar in the trials to placebo. (Med Lett Drugs Ther. 2020)

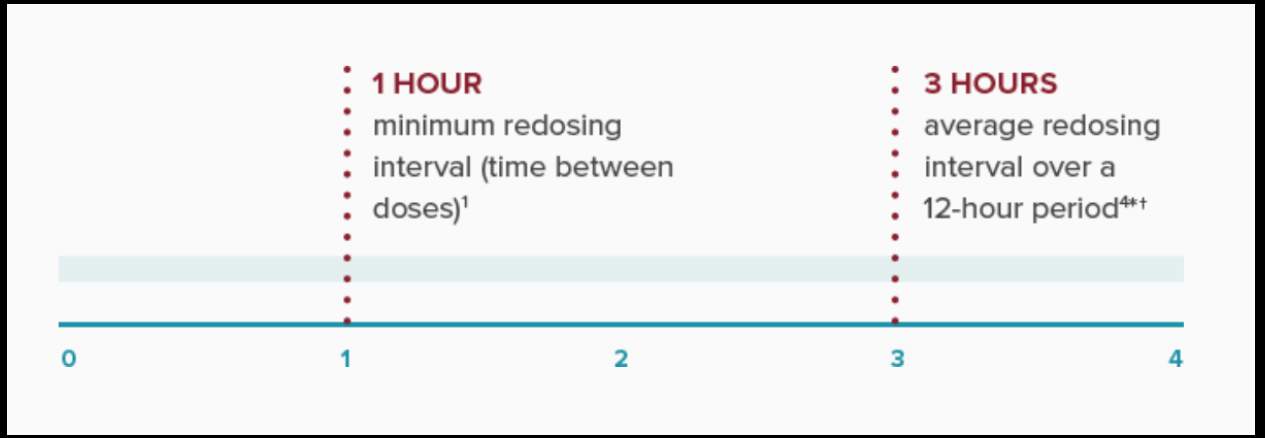


Sufentanil Sublingual

- In general PO opioids are preferred over IV opioids for pain control unless contraindicated.
- Sufentanil has been used for many years to treat acute pain, especially in the postoperative period.
- Sufentanil has now been formulated as a sublingual nanotab, sufentanil sublingual tablet system
- Dose is 30 mcg and the nanotab is in a single dose slide. (Giaccari, 2020)

Sufentanil Sublingual

- Sufentanil is selective for the mu-opioid receptor
- Potency is 7-10 times greater than fentanyl and 500-1000 times greater than morphine. High therapeutic index.
- Onset of SSTS is 15-30 min. Analgesic benefit ranged 2-24h.
- In a recent review of 16 studies for 2311 patients who were dosed with the SSTS, patient satisfaction was high. The most common AE were nausea, vomiting and headache. In general the data supports the efficacy and safety of the SSTS system. (Giaccari, 2020)
- Intended to treat moderate-to-severe pain.



Orphengesic Forte

- Multimodal therapy has become more important than ever given the current opioid issues.
- By relying on different non-opioid agents, mechanisms can be combined to provide analgesic efficacy without the risk of opioid side effects. Actually, multimodal non-opioid therapy has been shown to be superior to opioid monotherapy in terms of safety and tolerability.
- Orphengesic Forte consists of 50mg orphenadrine citrate, 770mg of Aspirin, and 60mg of caffeine. Previously marketed as Norgesic Forte.

Orphengesic Forte

- Orphengesic Forte is approved for the symptomatic relief of mild to moderate pain of acute musculoskeletal disorders, such as tension-type headaches, low back pain, and strains. (Pergolizzi, 2019)
- Orphengesic is an anticholinergic antihistamine, closely related to diphenhydramine.
  - It also has muscle relaxing properties and selectively blocks facilitatory functions of the reticular formation. (eg. Motor coordination, muscle tone, pain signaling).
- ASA is a well known NSAID that reduces inflammation

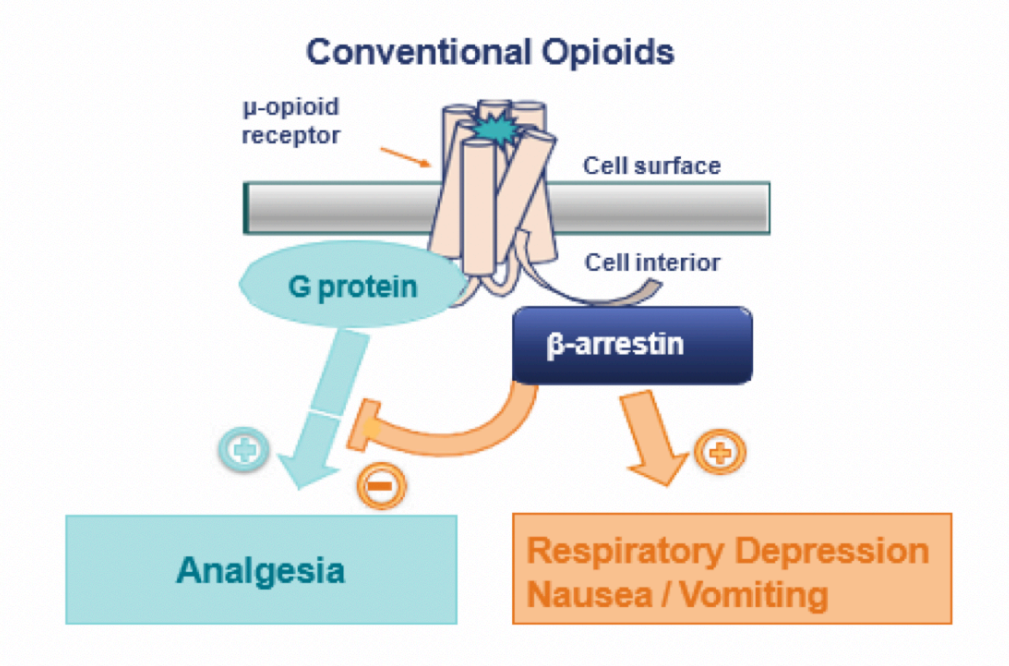
Orphengesic Forte

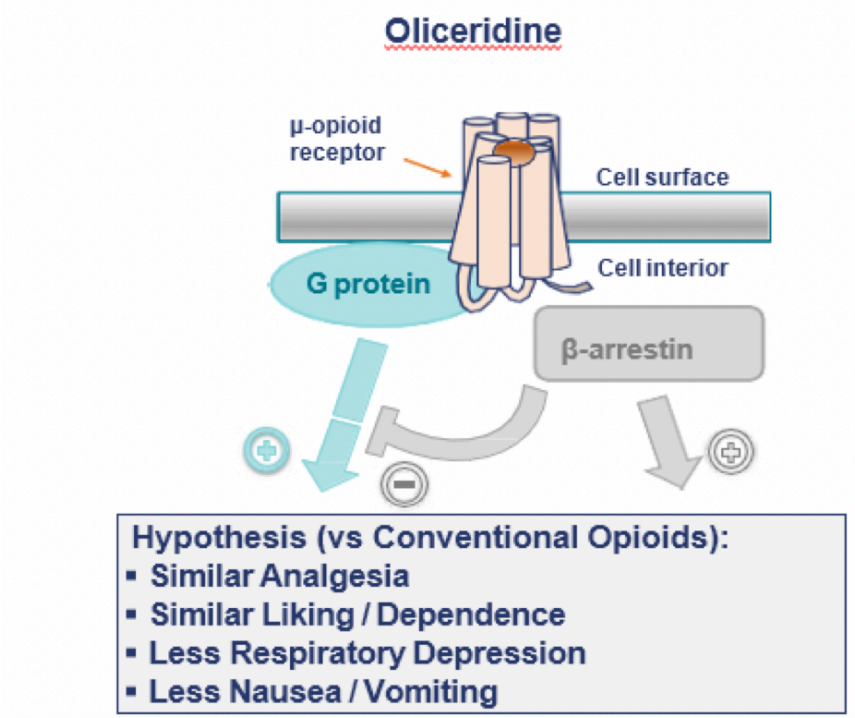
- Caffeine provides an analgesic synergistic effect by blocking adenosine receptors in the CNS and PNS.
- This medication does not directly relax tense muscles, and the mode of action of orphenadrine has not been clearly identified.
- The combination drug is contraindicated in patients with glaucoma, pyloric or duodenal obstruction, achalasia, prostatic hypertrophy, obstructions at the bladder neck, myasthenia gravis, hypersensitivity to the drug, and known sensitivities to aspirin or caffeine.
- Dosing is 1/2 tab-1 tab, 3-4 times a day for pain.

Oliceridine

- Oliceridine is the first G protein-selective agonist and was designed to deliver an improved analgesic profile compared to IV morphine for the management of moderate to severe acute pain.
- Mu-opioid receptor agonist elicits G protein signaling, with similar potency and efficacy to morphine, but with much less beta-arrestin 2 recruitment and receptor internalization, which may result in fewer adverse effects
- Oliceridine is indicated for short-term intravenous use in hospitals or other controlled clinical settings, such as during inpatient and outpatient procedures. It is not indicated for at-home use. (Approved 8/7/2020)

Oliceridine





Oliceridine

- An initial dose of 1.5 mg is recommended
- For PCA, recommended demand dose is 0.35 mg, with a 6-minute lock-out.
- A demand dose of 0.5 mg may be considered
- Supplemental doses of 0.75 mg oliceridine can be administered, beginning 1 hour after the initial dose, and hourly thereafter as needed
- Onset of analgesic effect is expected within 2 to 5 minutes after the initial dose
  - Do not administer single doses greater than 3 mg
- Based on data collected in clinical studies, an initial 1 mg dose of oliceridine is approximately equipotent to morphine 5 mg
- The maximally recommended daily dose limit for oliceridine is 27 mg

Oliceridine

- It appears oliceridine may be associated with a better AE profile compared to some opioids such as morphine.
- No dose adjustment is needed patients with renal impairment or mild-to-moderate hepatic impairment.
- No dose adjustment is recommended based solely on age.
- Other possible advantages include a reduction in PONV and a potential reduction in the risk of respiratory depression. (Gan, 2020)

Oliceridine

Safety Parameter	Study	Oliceridine 0.1 mg	Oliceridine 0.35 mg	Oliceridine 0.5 mg	Morphine
Respiratory Safety Event	Hard Tissue	1	9	14	18
	Soft Tissue	8	22	23	27
Oxygen Saturation < 90%	Hard Tissue	4	10	14	20
	Soft Tissue	8	19	20	24
Supplemental O_2	Hard Tissue	1	9	13	17
	Soft Tissue	8	20	23	28
Dosing Interruption	Hard Tissue	1	8	13	20
	Soft Tissue	7	22	23	29

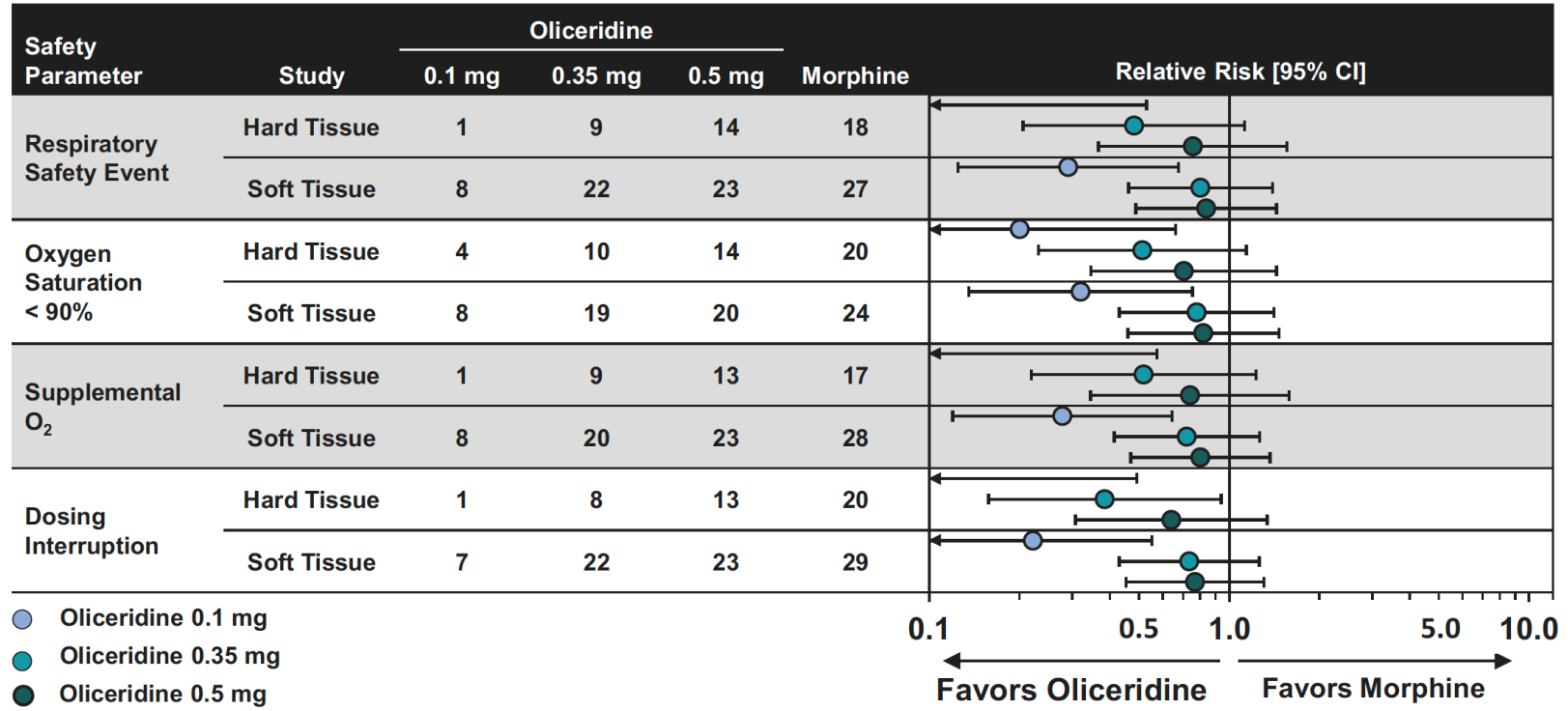


Figure 5. Respiratory safety events (RSEs) and clinical interventions in the pivotal studies APOLLO-1 and APOLLO-2 (39, 40). RSEs included clinical observations of changes in respiratory rate, oxygen saturation or sedation measured using the Moline-Roberts Pharmacologic Sedation Scale.

Gan, 2020

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