The Opioid Receptor: Recent Discoveries and New Opportunities

National Center for
WELLNESS & RECOVERY
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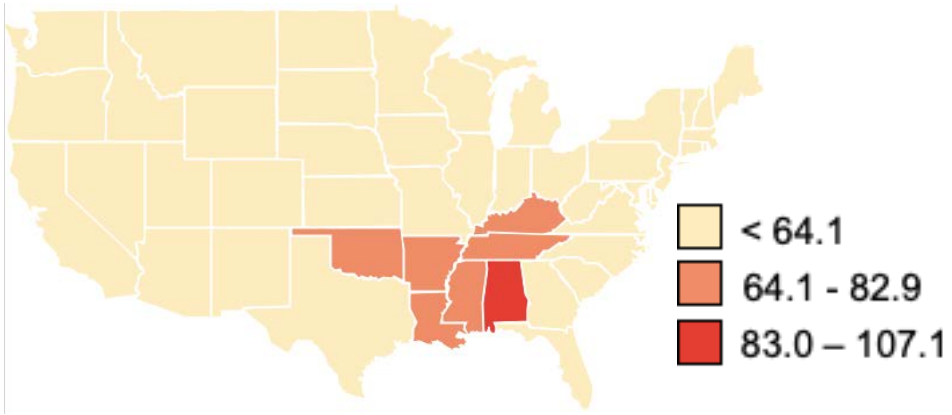
Humans and Opium: A Very Long History

- Assyrian tablets & carvings may reference “opium” (~4000 BCE)
  - Cradle of civilization
  - Within the “fertile crescent”
  - Herbal medicinal recipes
- Ebers Papyrus, one of the oldest medical texts (1550 BCE)
  - ~700 prescriptions, “sponges soaked in opium for surgical pain”
- Neolithic burial caves contain opium poppy capsules & seeds
  - Direct dating reveals the early history of opium poppy in Europe. *Sci Rep* **10,** 20263 (2020)
- Opium poppy adapts easily to varying soil types & climate

Opioids: The Gold Standard for Pain Relief

Total Number of Opioid Prescriptions Dispensed per 100 Persons (US, 2019)

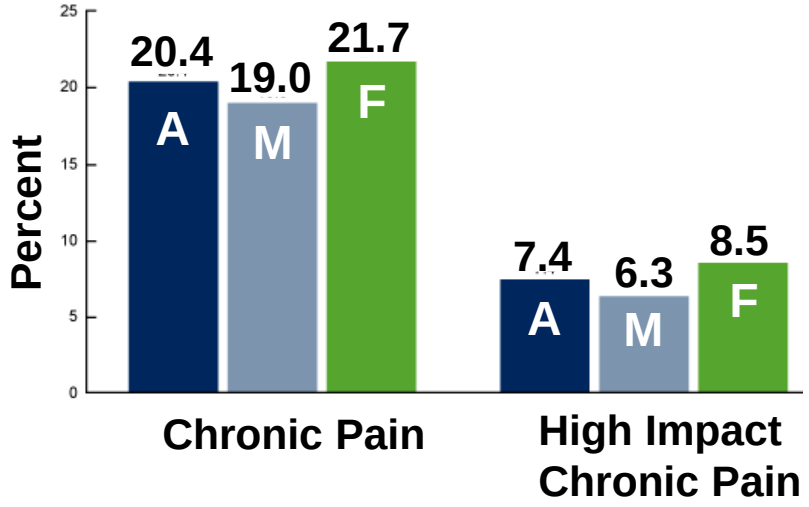
Centers for Disease Control and Prevention, National Center for Injury Prevention and Control



Year	Total Prescriptions	Dispensing Rate Per 100 Persons
2015	226,819,924	70.6
2016	214,881,622	66.5
2017	191,909,384	59.0
2018	168,158,611	51.4
2019	**153,260,450**	**46.7**

Chronic Pain and High-impact Chronic Pain Among U.S. Adults, 2019

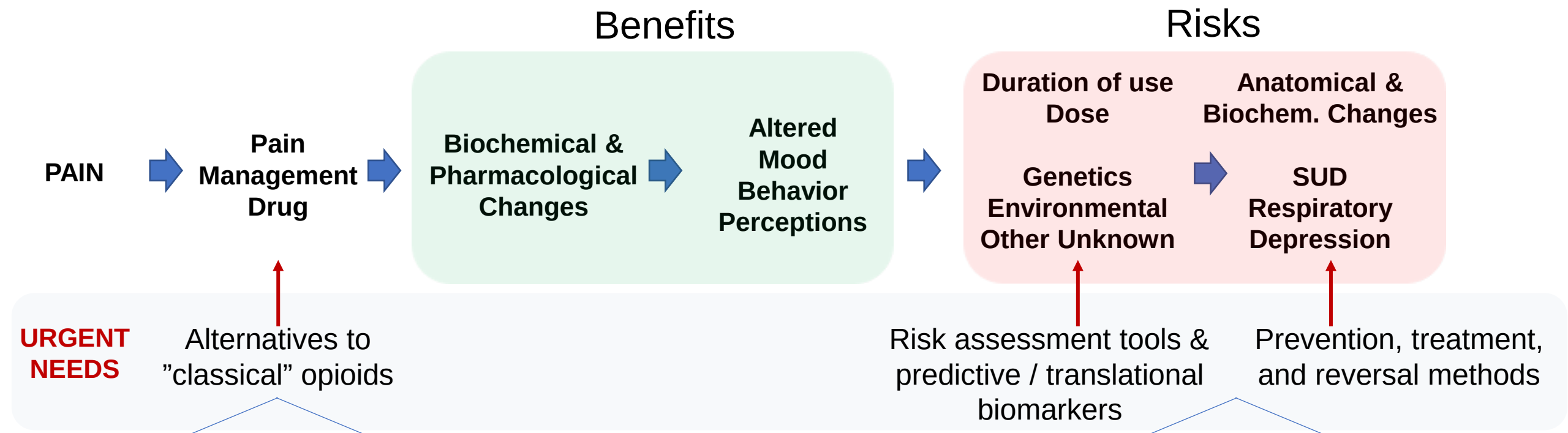
NCHS Data Brief No. 390, November 2020. Carla E. Zelaya, *et a*l.



Key findings

- 20.4% of adults had chronic pain and 7.4% had chronic pain that frequently limited life or work activities.
- Percentage increased with age (highest among 65+ yrs).
- Non-Hispanic white adults more likely to have chronic pain.
- Percentage increased as place of residence became more rural.

NCWR Research: Ending Addiction Managing Pain



- Discovery and approval of new pain medications has been disappointing.
  - Pain perception is subjective
  - Placebo effects are common
  - Poor translation from animal models to human

- Complex addiction mechanisms not well understood.
  - Genetics
  - Biochemistry
  - Behavioral

Opioid Chemistry and Biology Don't Overlap in History

Era of Chemistry

~5800 BCE

Opium Latex

1804

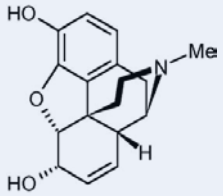
Morphine From Opium

Heroin 1874

1916
1920

Oxycodone Hydrocodone

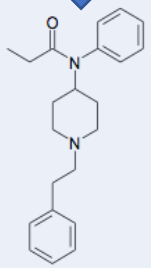
1925



Morphine Structure

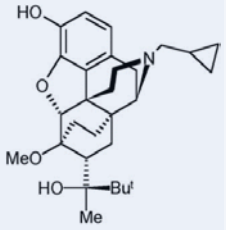
1932

Meperidine



Fentanyl 1959

1965



Buprenorphine

Era of Biology

1970

Mu Receptor Identified

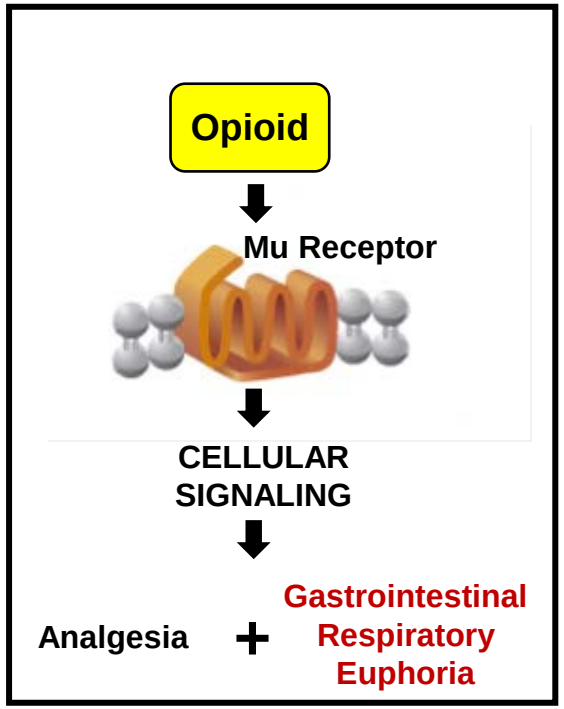
Present

- Biotech Advancements
- Scientific Instrumentation
- GPCR Cryomicroscopy
- Signal Transduction

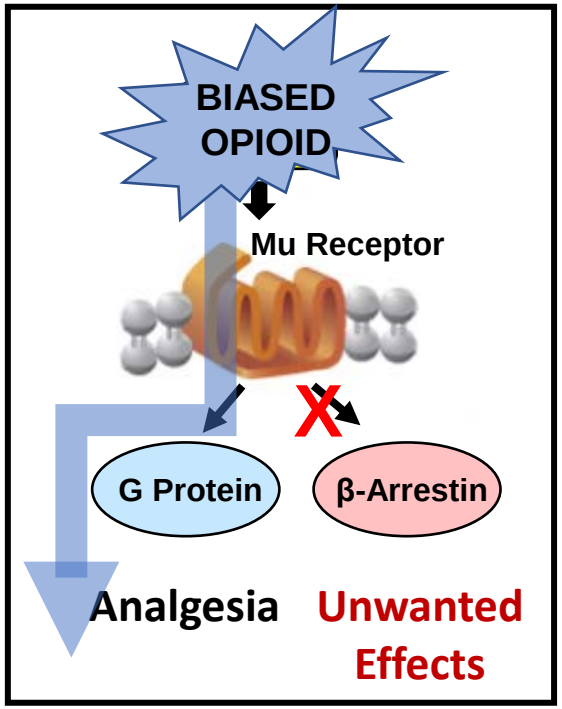
- Prescription opioids used today were discovered without the benefits of modern drug discovery technologies.
- Are "classical opioids" optimized?

Pain Research: Revisiting the Mu Receptor

Opioid Pharmacology



New Opioid Pharmacology

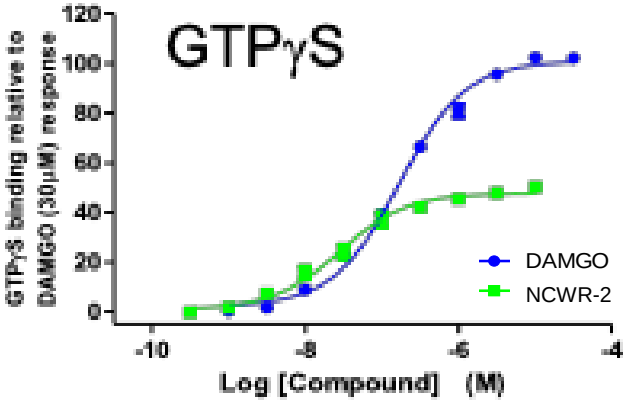


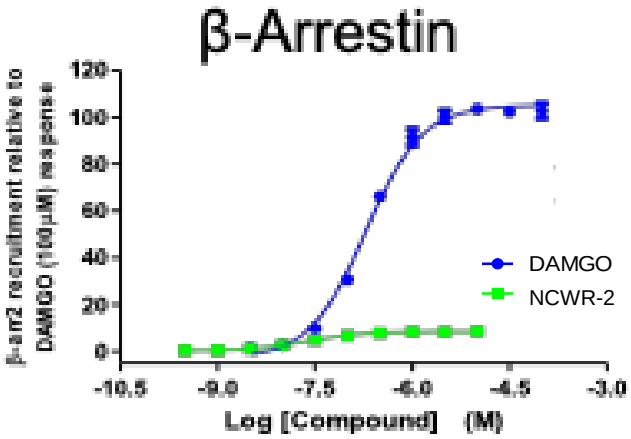
It is usually presumed that opioid analgesia and unwanted effects are inseparable.

New “biased opioid” research molecules at NCWR show analgesic efficacy with reductions in unwanted effects in animal models.

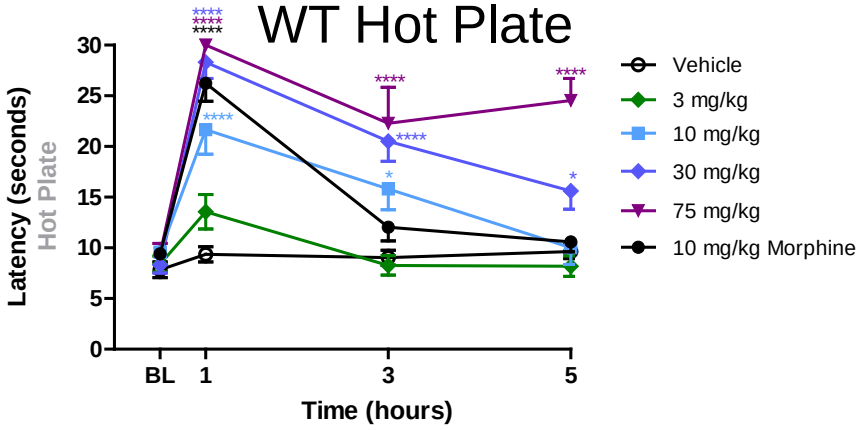
NCWR-2: A Novel Biased Mu Agonist

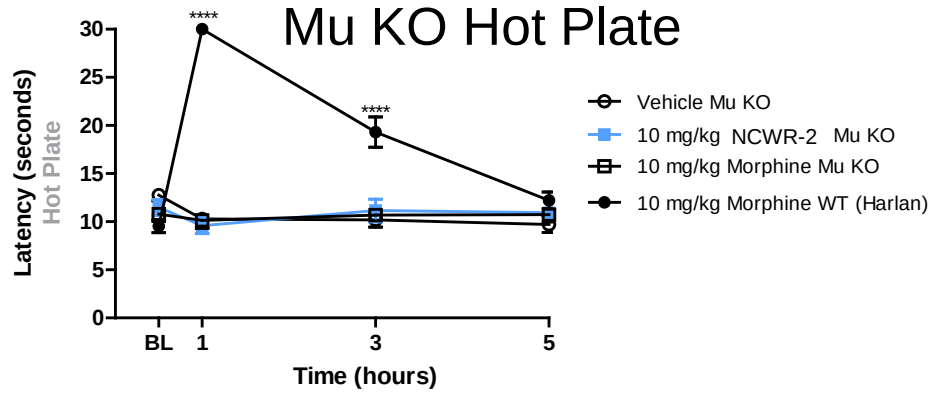
In vitro Pharmacology



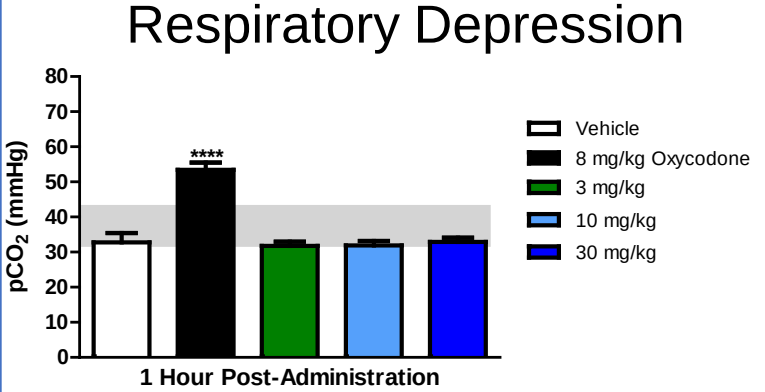


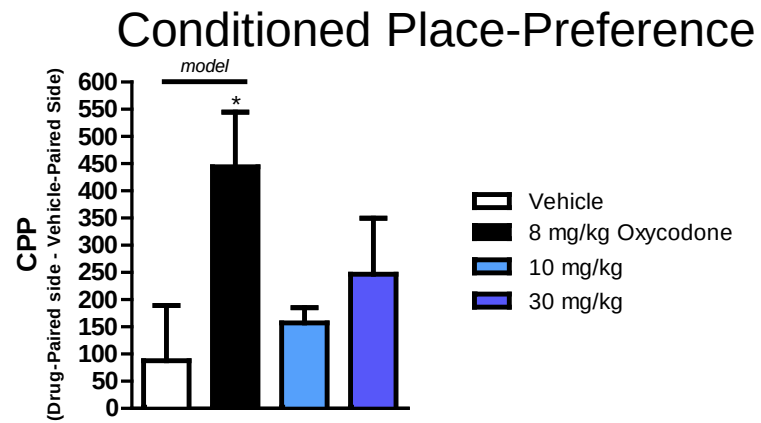
In vivo Efficacy





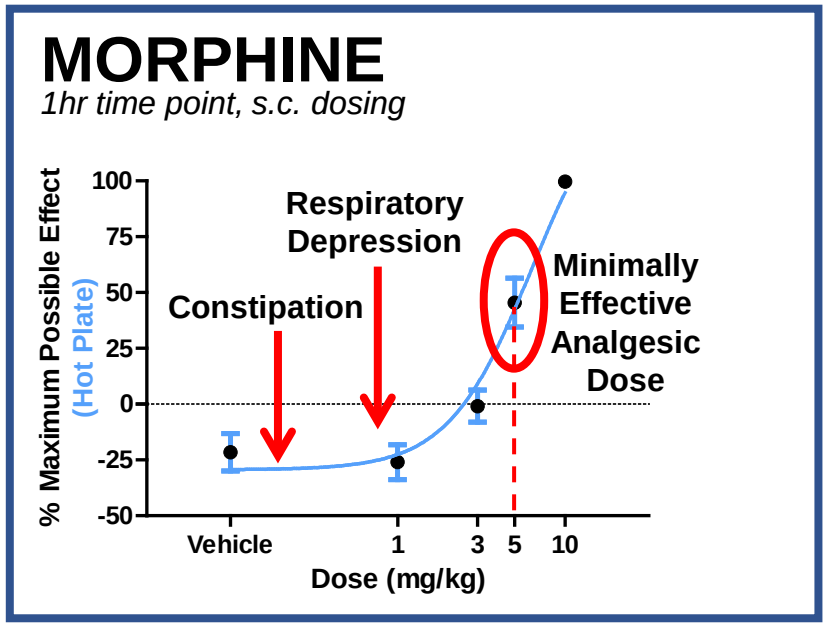
In vivo Side Effects

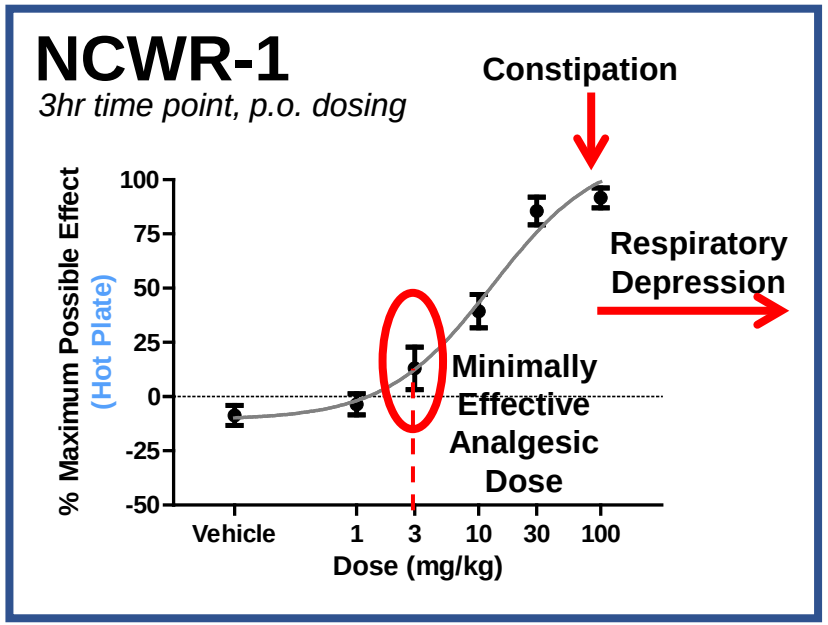


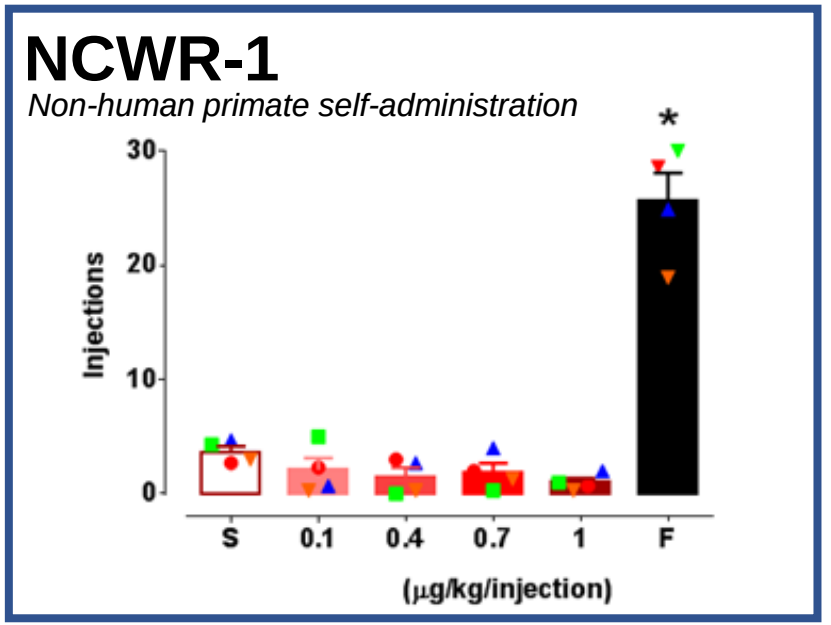


NCWR-1: Promising Side-Effect Profile of a Novel Biased Mu Agonist

Self-Administration







NCWR-1 is treated like **S**aline, not like **F**entanyl

- The onset and severity of important opioid side-effects differ significantly between classical opioids and the novel NCWR molecules.

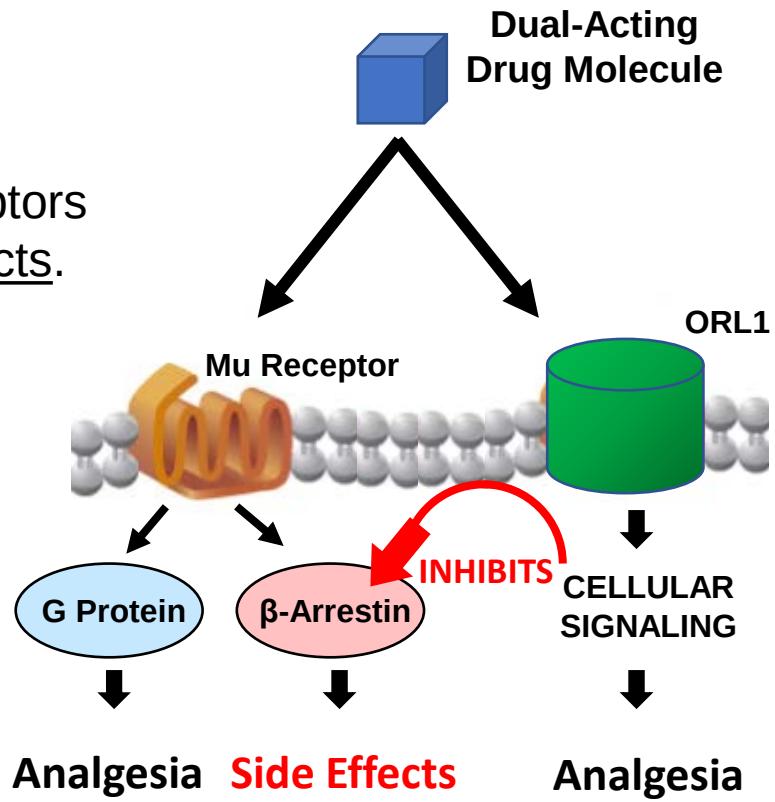
- NCWR is advancing the science of "biased opioid agonists" that will hopefully provide new options for physicians and benefits patients.

Poly-Pharmacological Opioid Mechanisms

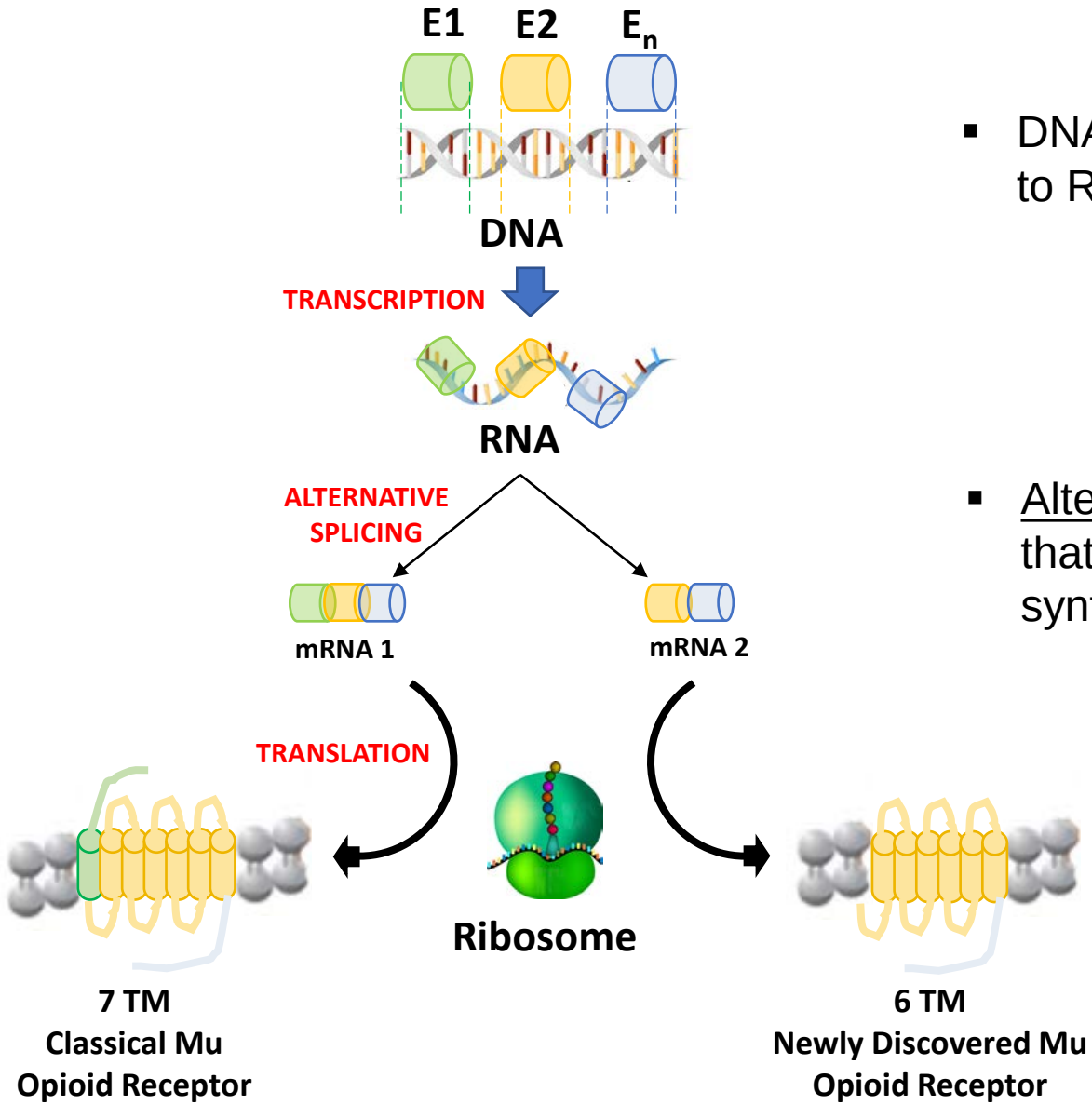
- Mu receptors are not the only thing on cell membranes.
- Designing a drug molecule that binds and stimulates multiple receptors might produce additive analgesia and reduced/eliminated side effects.
- Dual-acting molecules under investigation at NCWR include:

  Mu/ORL1
  Mu/Kappa
  Mu/TRPV1

- With these new molecular tools, NCWR researchers are at the forefront of another new approach toward safer pain medications.



Splice Variants of the Mu Opioid Receptor

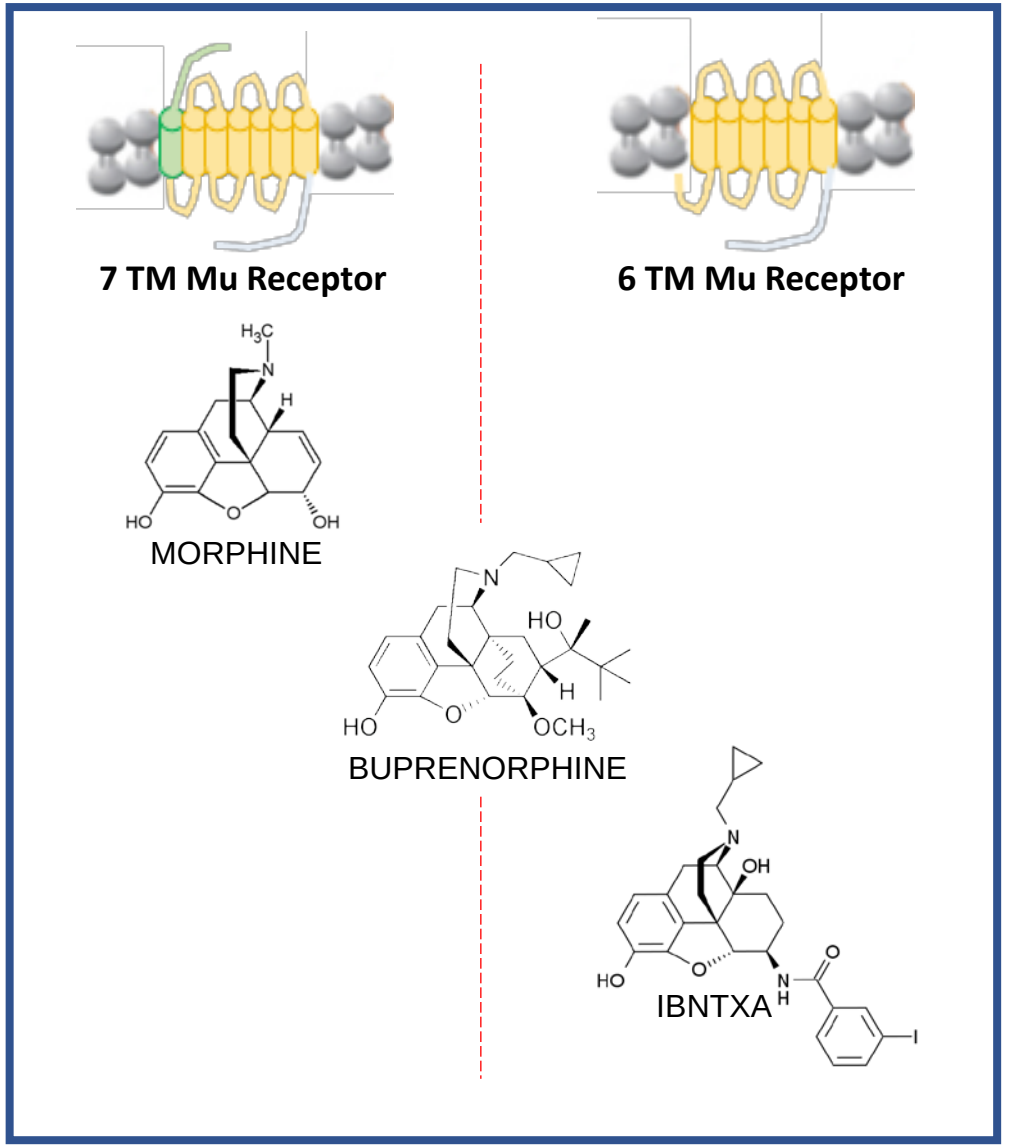


- DNA contains discreet segments known as exons that are copied to RNA during transcription.
- Alternative splicing of exons leads to multiple mRNA sequences that are read by the ribosome during translation and protein synthesis.
- There are two major alternative splice variants of the mu opioid receptor known as the 7 TM form and the 6 TM form.
  - Amino acid sequence differences may alter the drug binding site and intracellular signaling!

Emerging Significance of Mu Receptor Splice Variants

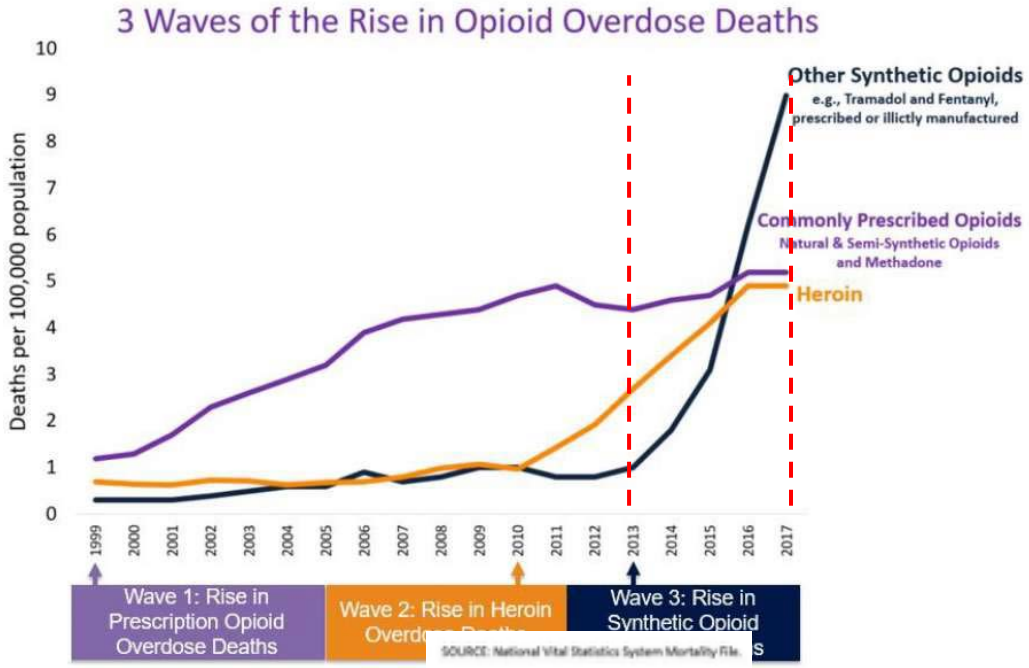
POSSIBLE NEW DRUG TARGETS FOR PAIN

- Known opioids have differences in binding affinities to the two receptor forms and they signal differently in cells.
- The recently discovered molecule IBNtxA is selective for the 6TM form of the mu receptor.
  - No evidence for respiratory depression in animals
  - No inhibition of GI transit
  - No place preference
  - Potent analgesia
- Human genetic differences likely alters expression of the two forms, possibly contributing to different responses to opioid drugs.
- Chronic exposure to opioids causes increased expression of the 6 TM form of the receptor and decrease of 7 TM form.
- 6TM mu receptor heterodimerizes with other receptor(s), for example β_2-AR to form an interesting new drug target.



New Pharmacological Tools Against the Emerging Fentanyl Crisis

- The 3rd wave of the opioid crisis is fueled by fentanyl
- Fentanyl is particularly dangerous
  - Mu receptor affinity and duration of action exceed naloxone
  - Very fast CNS penetration
  - ”Designer” analogs of fentanyl are evasive to law enforcement
  - Inexpensive to prepare without need of opium poppies
  - Blended into other drugs of abuse without knowledge of the user.



	Affinity	Potency	Efficacy	CNS Penetration	Duration
Molecule	Mu Opioid Receptor			Lipophilicity	Half-Life
	K_i (nM)	GTPγS EC_{50} (nM)	GTPγS E_{MAX} (%)	AlogP	Hours
Fentanyl	2.7	133	88	4.05	4-8
Naloxone	8.8	>20000	0	2.1	0.5 – 1.5

- Novel research molecules at the NCWR have profiles that may lead to effective alternative treatments for fentanyl overdose
  - Selective binding to mu opioid receptor
  - Higher affinity to mu opioid receptor than naloxone
  - High CNS penetration
  - Long duration of action

Biomarker Research at the NCWR

- NCWR has access to nearly 50,000 bio-samples from consenting patients.
  - Samples from ~30 Phase 2-3 clinical trial protocols for pain
  - Tested drugs include opioids and non-opioids (time-course)
  - Blood, DNA, and RNA cross-referenced to non-confidential patient records
  - Adding additional bio-samples from MAT in the future

- Research strategies and identification of collaborators in progress.
  - Internal assessments of existing and future NCWR core competencies
  - Data mining and visualization tools are under consideration
  - Complementary scientific partners enhance and accelerate NCWR's mission

- Successful research will have broad and significant medical impact.
  - Translational bio-markers will stimulate new research for opioid alternatives
  - Pain bio-marker to supplement self-report in clinical trials may improve outcomes
  - Predictive bio-markers for risk and/or onset of addiction highly beneficial

Summary

- Human experience with opium dates to the 6th millennium BCE, but the goal of separating analgesia from unwanted side effects remains today.
- It is disappointing that opioids, some over 100 years old, remain as the gold standard pain medications despite the significant technological advances of our time.
- The discovery of new types of opioid agonists known as biased agonists and poly-pharmacological agonists show promising potential as new therapeutics and are valuable research tools.
- Splice variants of the mu opioid receptor (and heterodimers) may represent a new frontier for drug design of potent analgesics with minimal or reduced unwanted side effects.
- The National Center for Wellness and Recovery at OSU in Tulsa has unique assets and is expanding its research capabilities to advance the science of pain and addiction.