

Pain, opioids and the addiction crisis

Bronwyn Kivell
Associate Professor

U3A
April 30th 2019



Capital thinking. Globally minded.

Pain is a major problem worldwide




#1
reason to visit
the doctor



\$740
billion annually
in the US

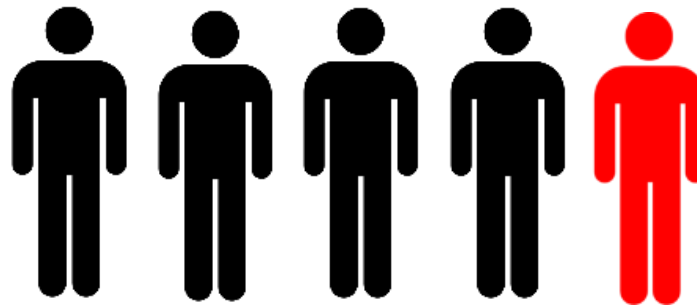


4.6hr
lost per worker
each week



R_x
191 million opioid
prescriptions

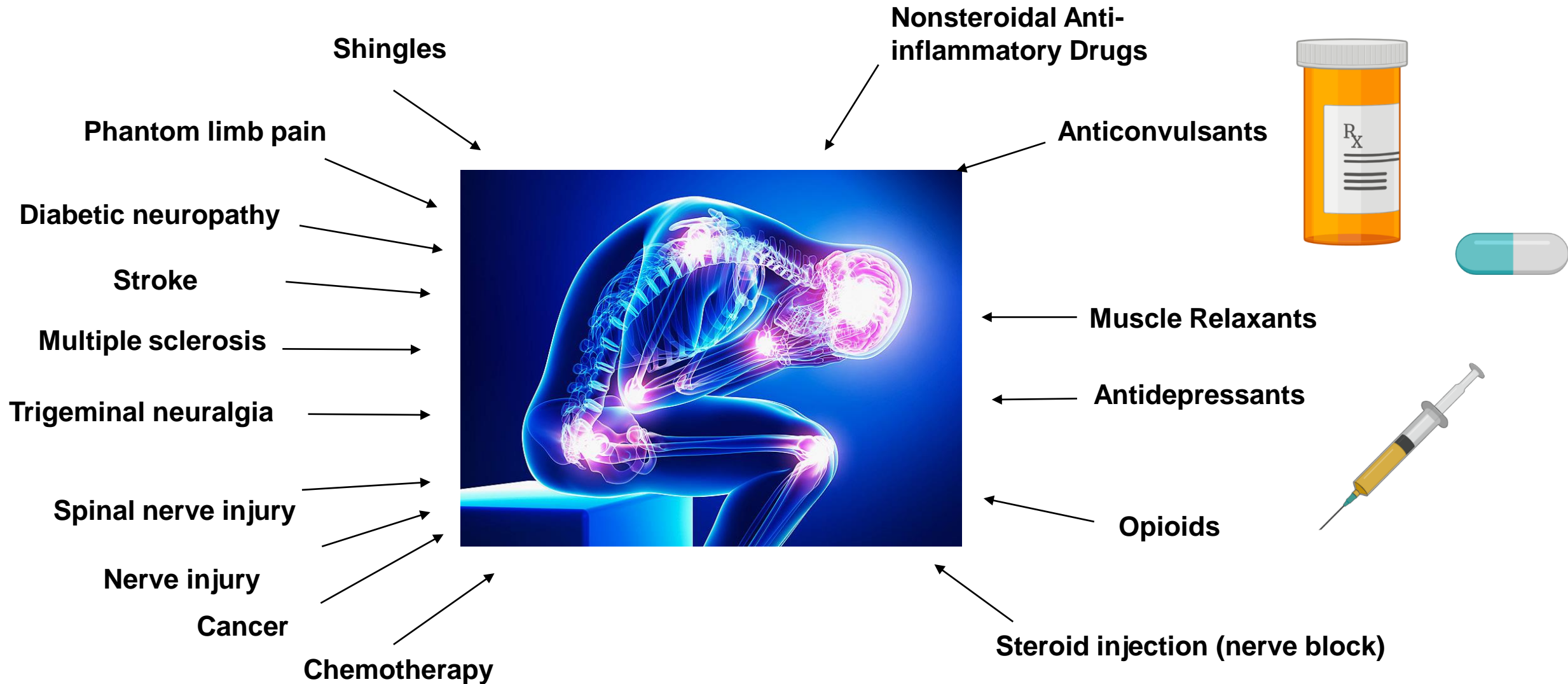
In NZ, 1 in 5 currently suffer from chronic pain



>700,000 adults in NZ
experiencing pain almost every

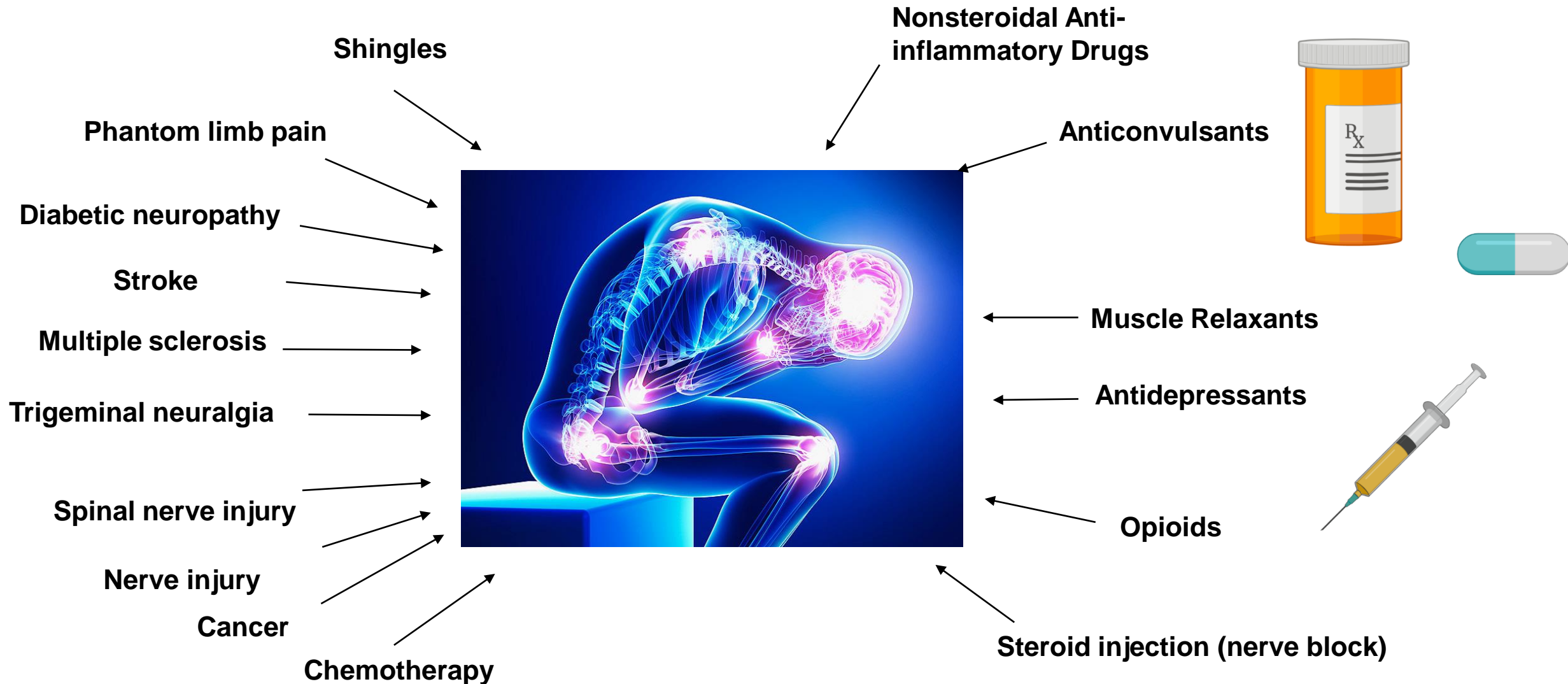
The development of effective analgesics remains a high priority

Chronic pain is complex

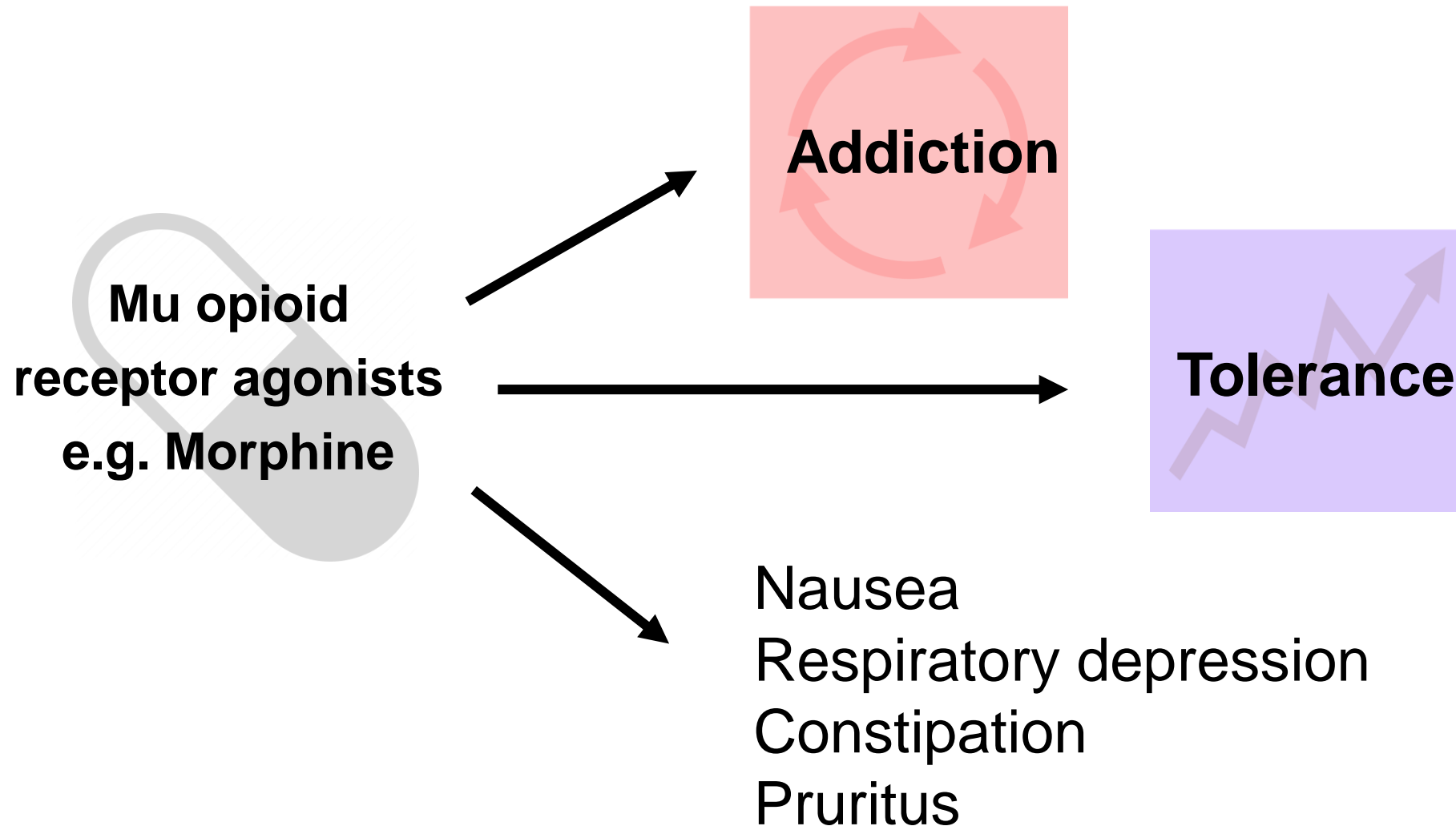


Chronic pain is complex

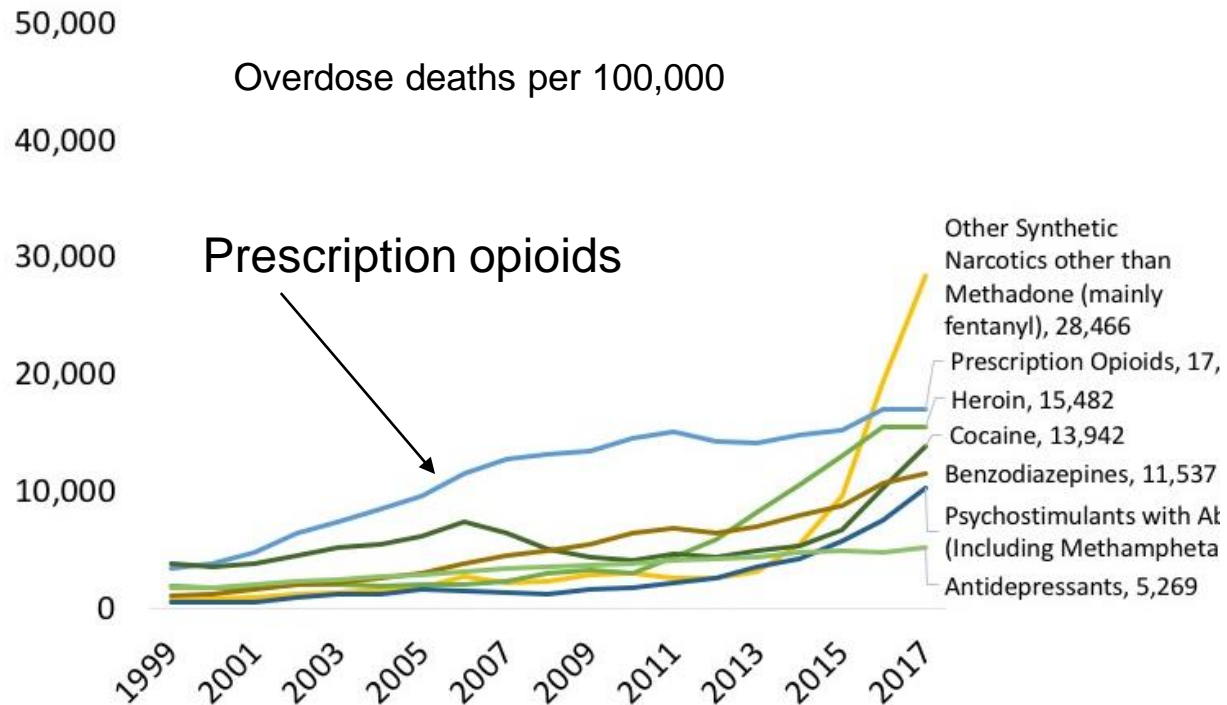
40% of chronic pain sufferers report insufficient pain control



The problem with current treatments

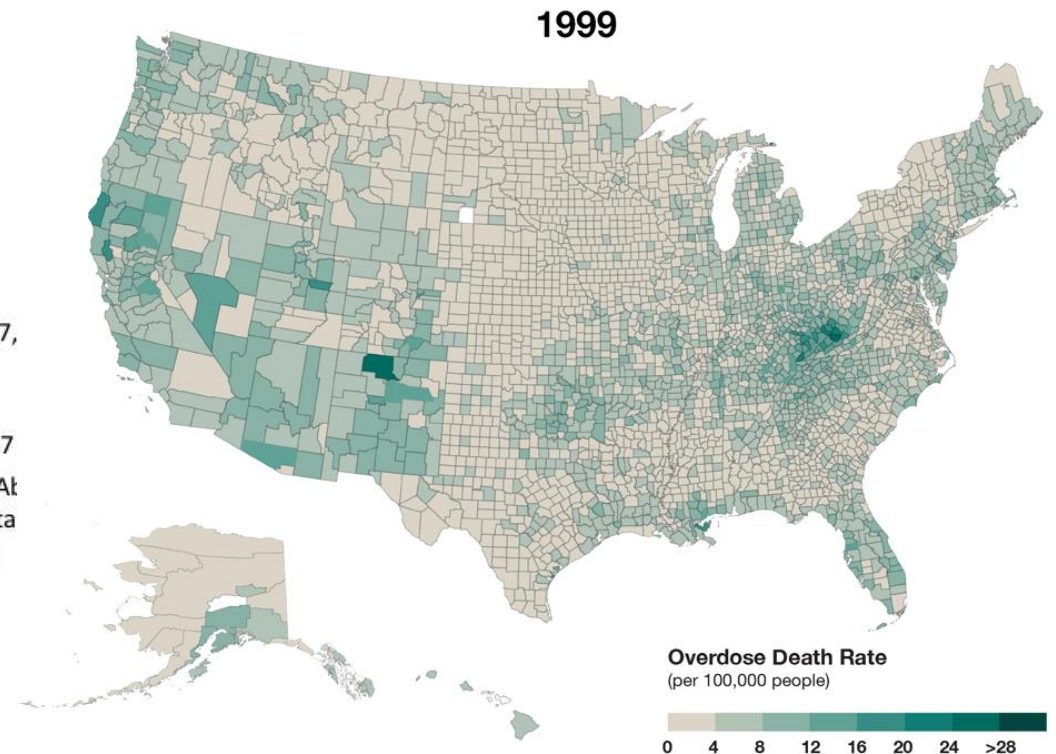


The opioid crisis



Source : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death Data, 1999-2017 on CDC WONDER Online Database, released December, 2018

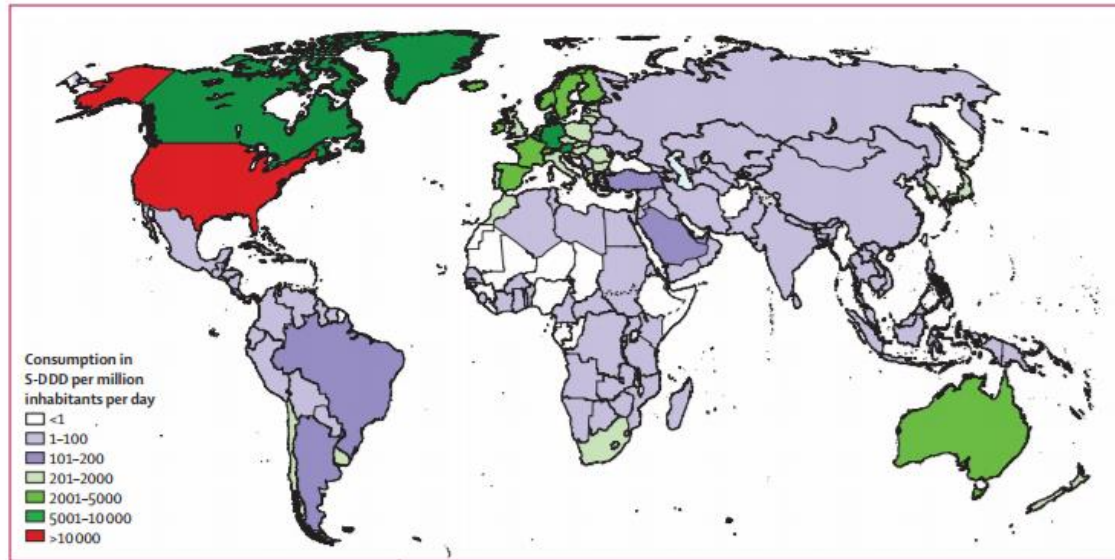
(NIH, 2019)



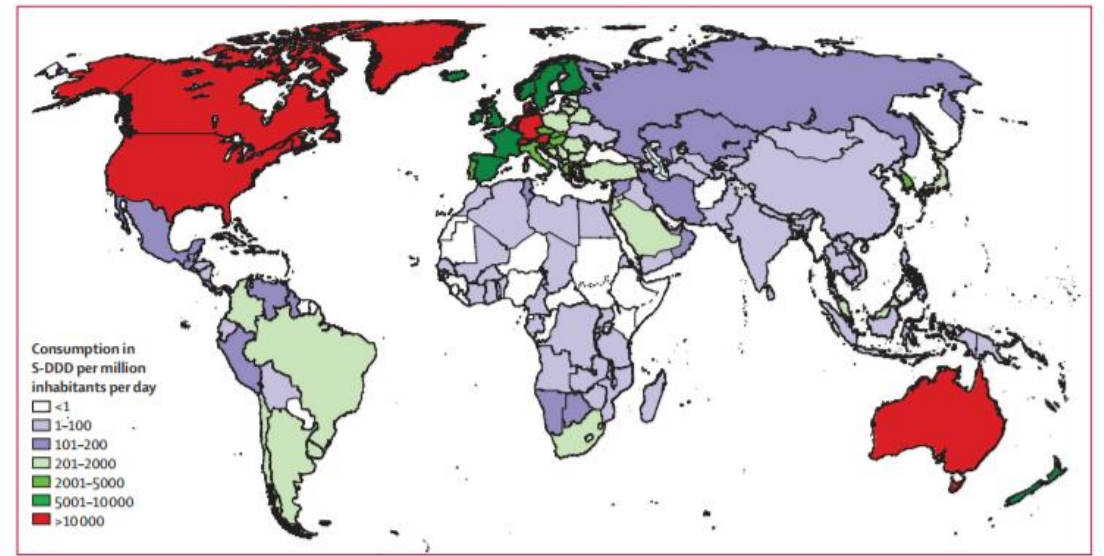
The Lowdown
County-level data on the opioid crisis

The opioid crisis

2001-2003



2011-2013

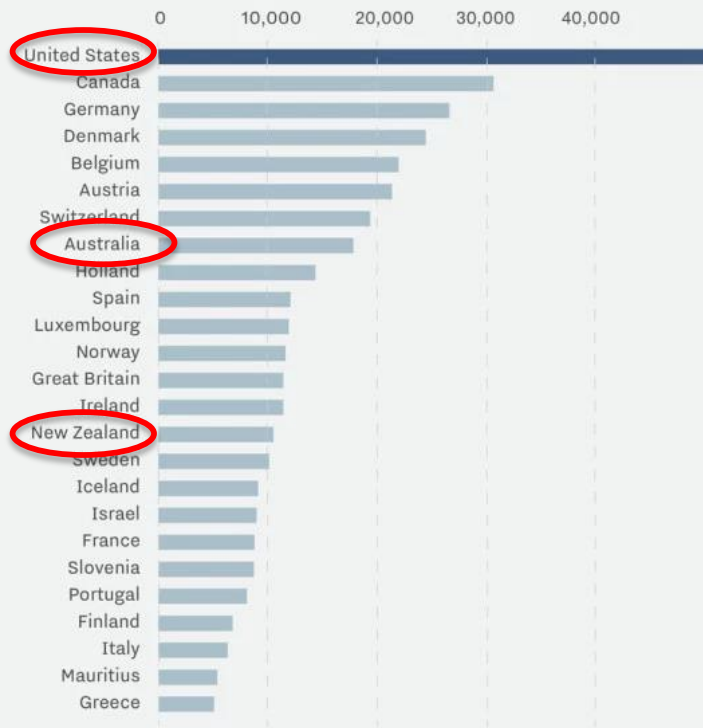


In NZ daily doses/million inhabitants has quadrupled

Australasian opioid use data

Americans consume more opioids than any other country

Standard daily opioid dose for every 1 million people



Source: United Nations International Narcotics Control Board
Credit: Sarah Frostenson

Vox

Fentanyl linked to 11 deaths in New Zealand since 2011

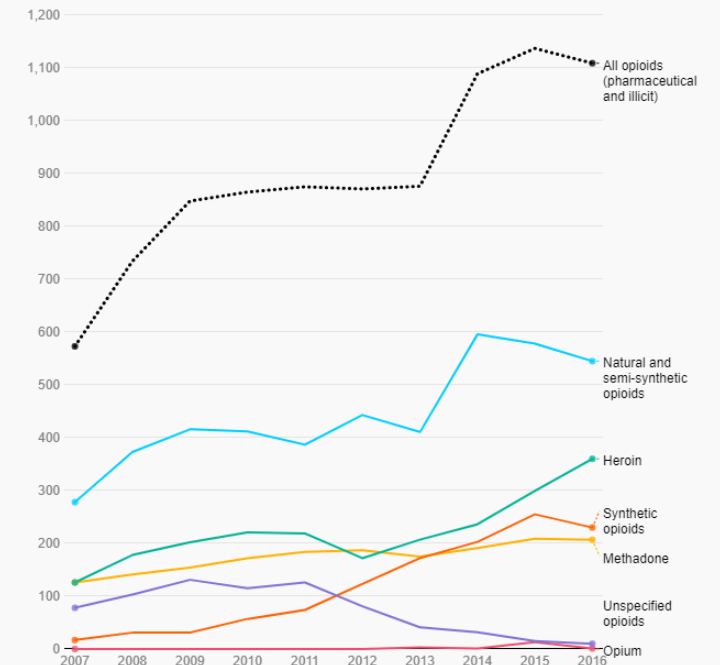
HANNAH MARTIN
Last updated 09:06, April 4 2018



Fentanyl has long been used in hospitals and hospices for care of chronically ill and dying patients: now it's been seen at a festival.

123RF

Fatal opioid overdoses in Australia



Deaths reported for each drug are deaths induced by that drug. Small numbers are randomly assigned to protect confidentiality of individuals; zero values are absolute. Numbers for 2015 and 2016 are preliminary and subject to revision.

Chart: ABC News • Source: National Drug and Alcohol Research Centre • Get the data • Embed

Research strategies to combat chronic pain

1. Are there better drug targets?



Research strategies to combat chronic pain

1. Are there better drug targets?

Conotoxins



Peptide	Amino Acid Sequence	Target
ω -MVIIA	CKGKGAKCSRLMYDCCTGSCRSKGK*	Ca ²⁺ channel (N-type)
ω -CVID	CKSKGAKCSKLMYDCCSGSCSGTVGRC*	Ca ²⁺ channel (N-type)
Conantokin-G	GEyyLQyNQyLIRyKS N*	NMDAR (NR2B)
Contulakin-G	ZSEEGGSNATKKPY IL	Neurotensin receptor
α -Vc1.1	GCCSDPRCNYDHP EIC*	nAChR (α 9 α 10)
χ -MrlA	NGVCCGYKLCHOC	Norepinephrine transporter

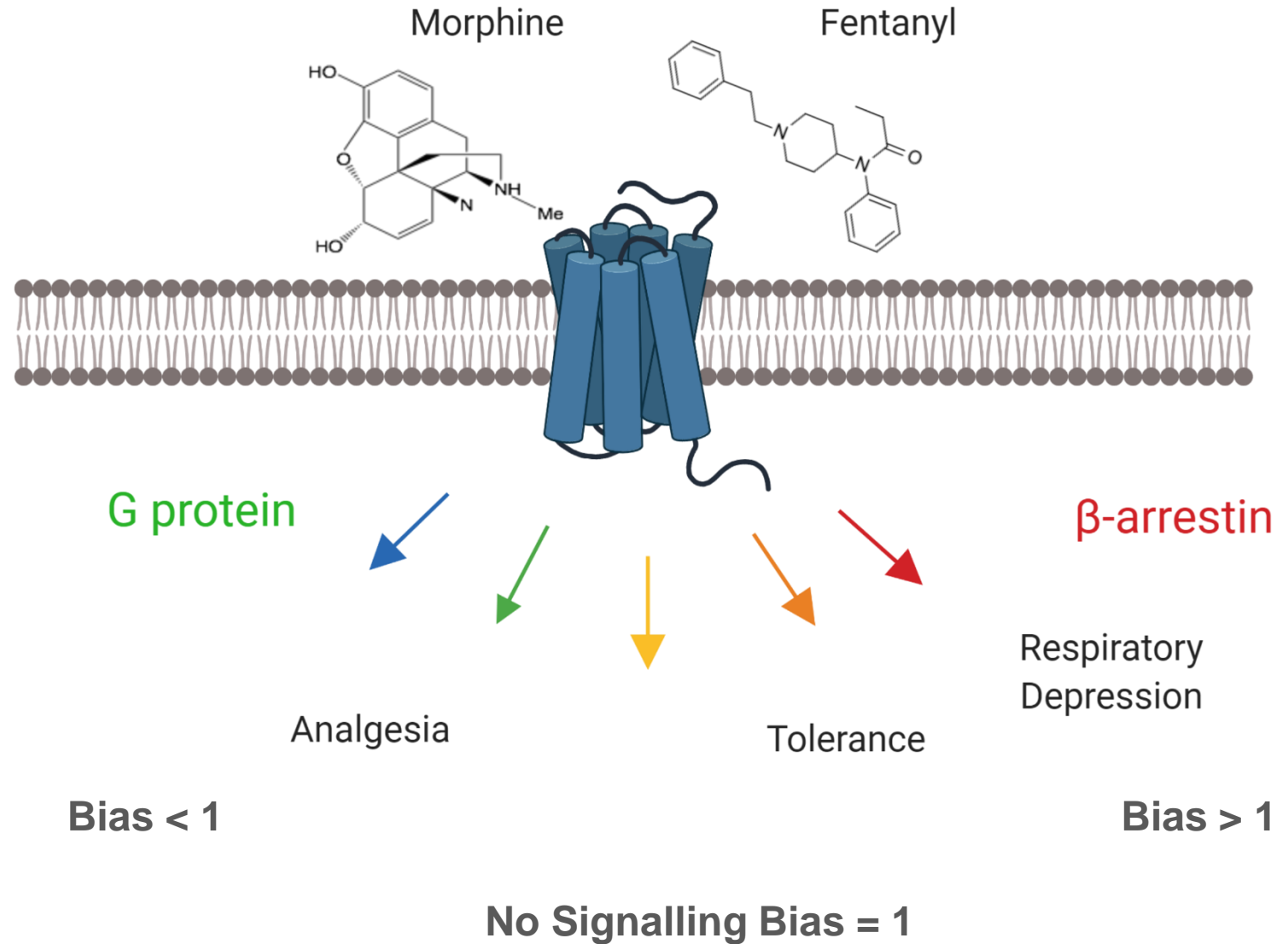


Research strategies to combat chronic pain

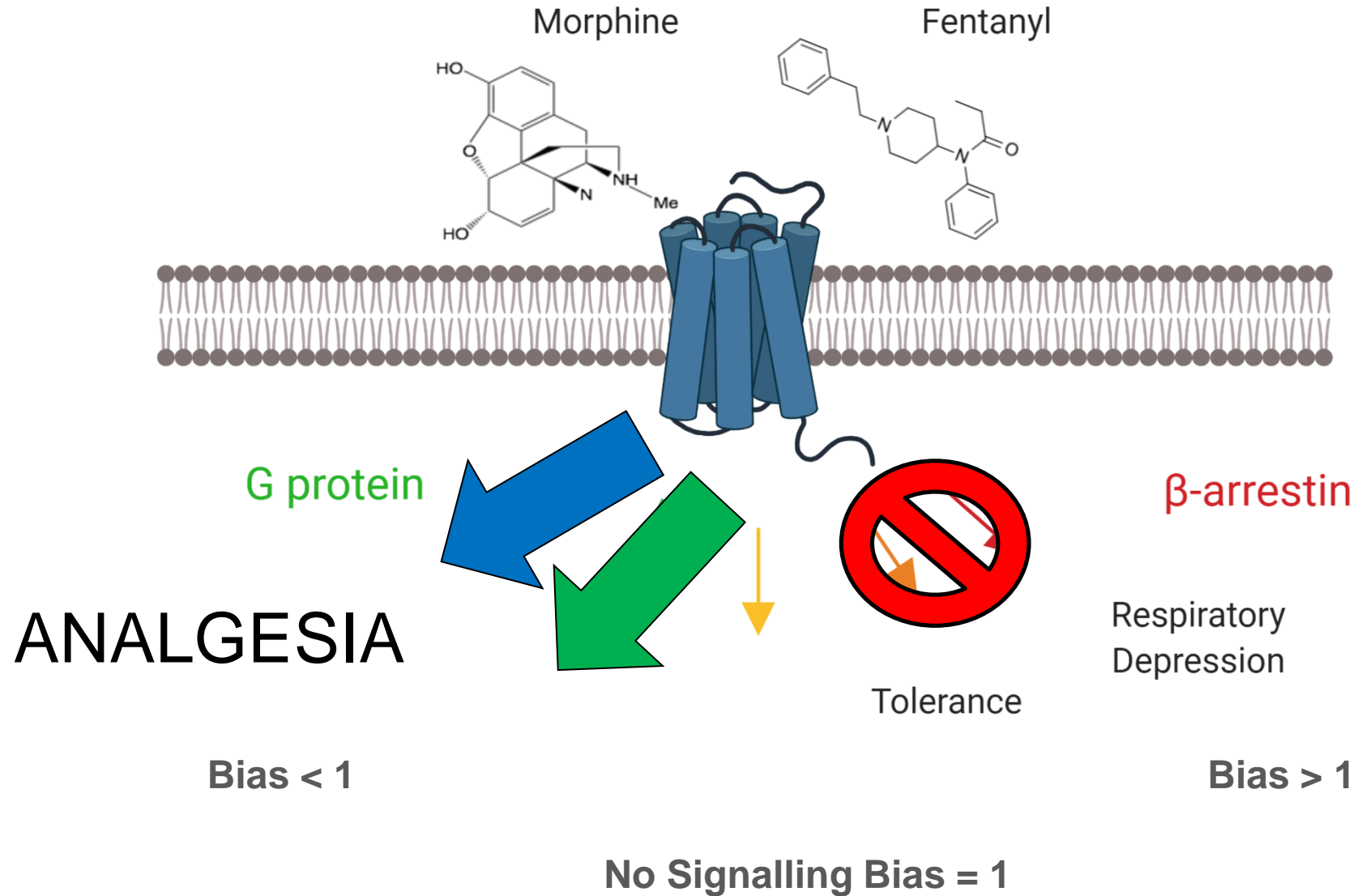
1. Are there better drug targets?
- 2. Can we make better drugs to existing targets?**



The theory of biased agonism



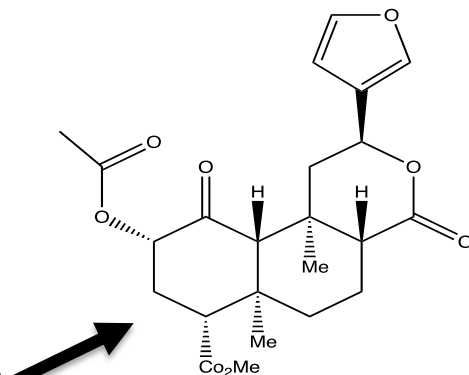
The theory of biased agonism



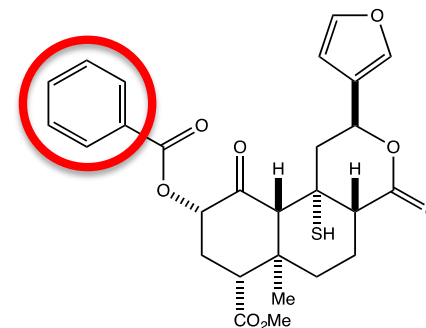
Novel mu-opioid agonists



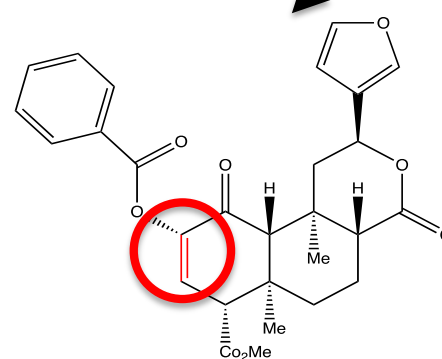
Salvia divinorum



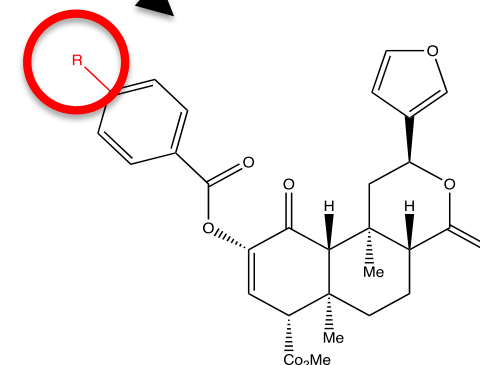
Sal A
EC₅₀ = 0.04 nM
κ/μ > 4.0 × 10⁻⁶



Herkinorin
EC₅₀ = 40 nM
κ/μ = 4.25



Kurkinorin
EC₅₀ = 1.2 nM
κ/μ < 8,000
Bias = 0.57

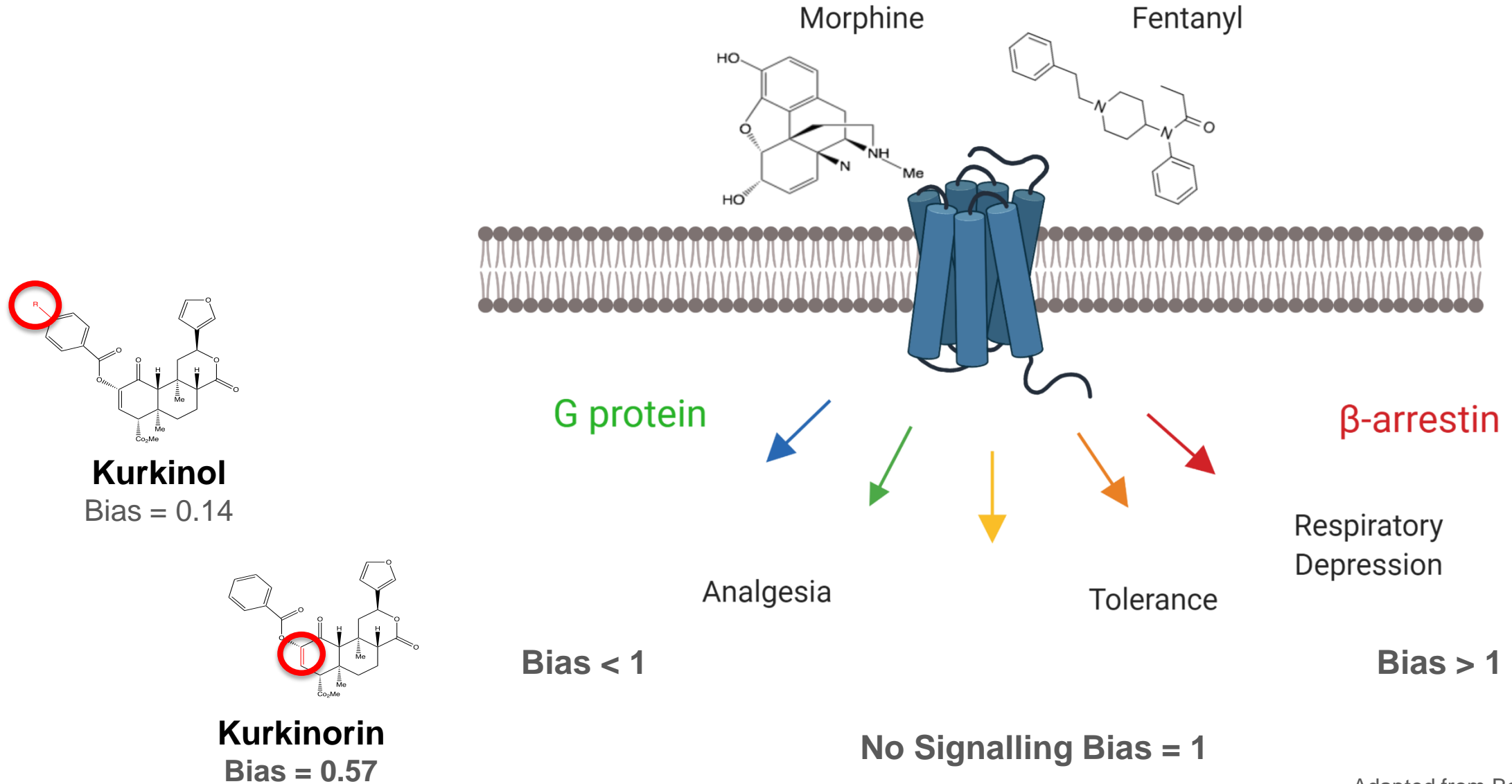


Kurkinol
EC₅₀ = 0.03 nM
κ/μ < 10,000
Bias = 0.14

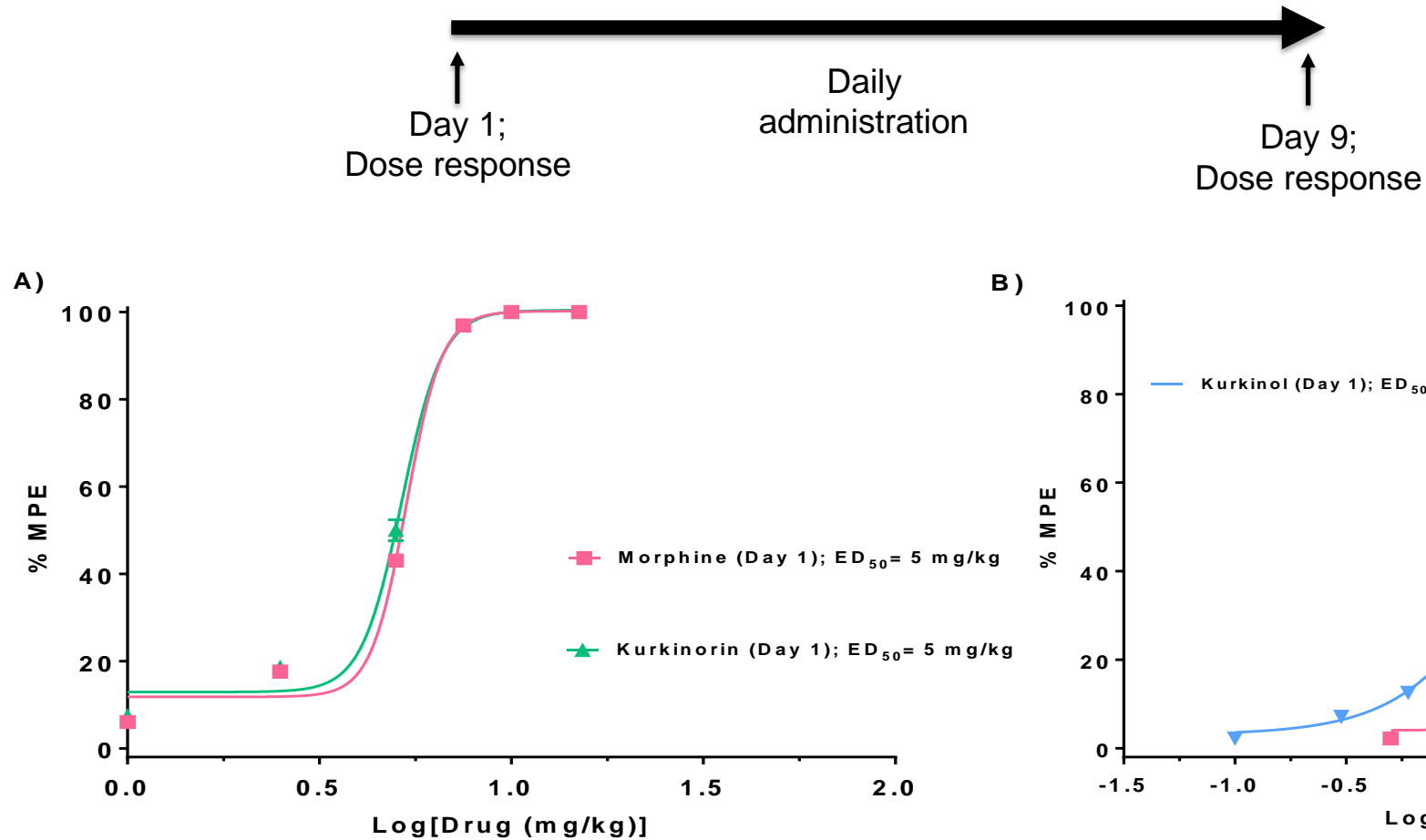
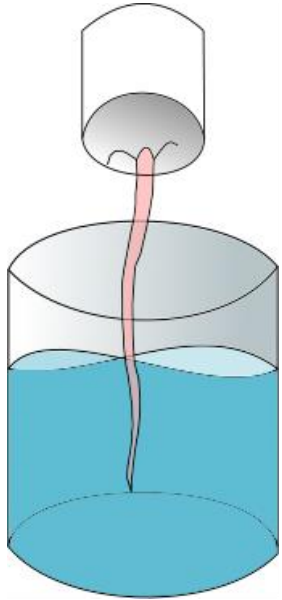


Prof. Tom Prisanzano
Dr Rachel Crowley
Sam Williamson

G-protein biased mu-opioid agonists

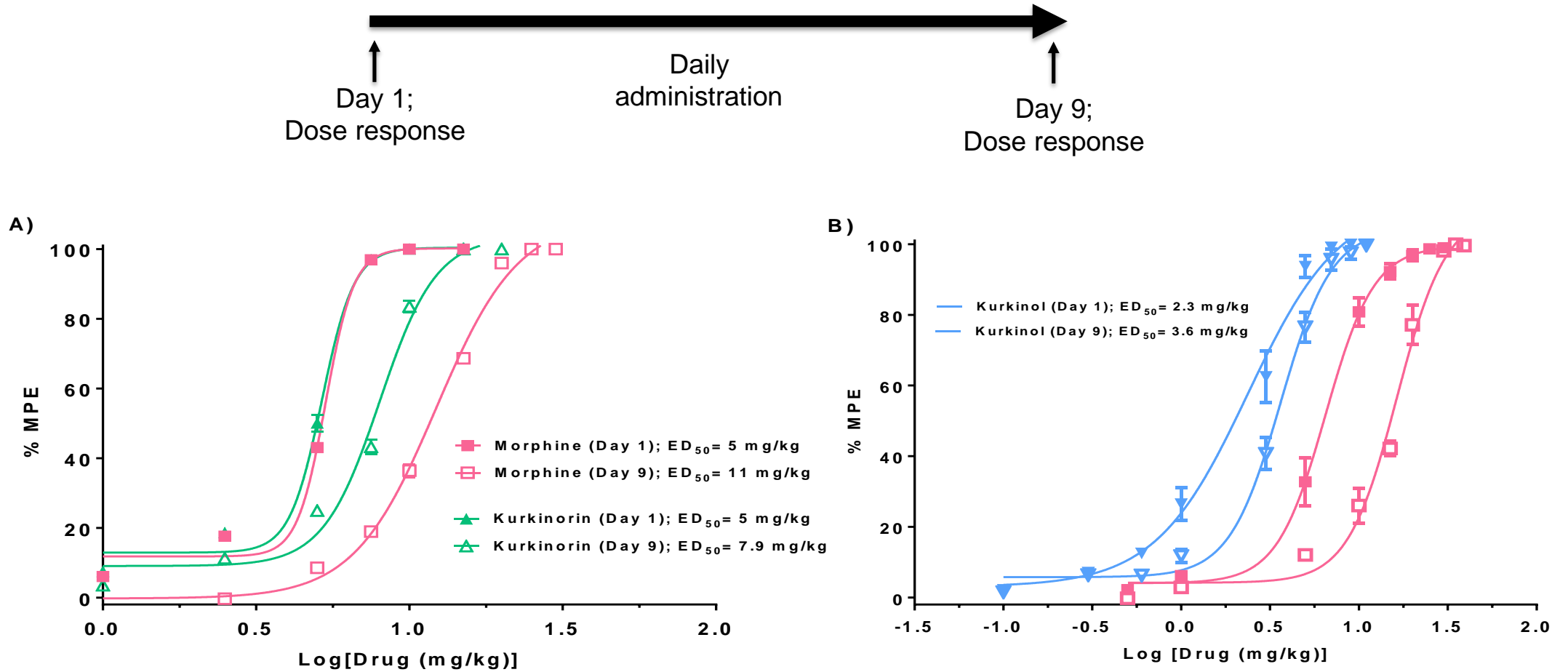
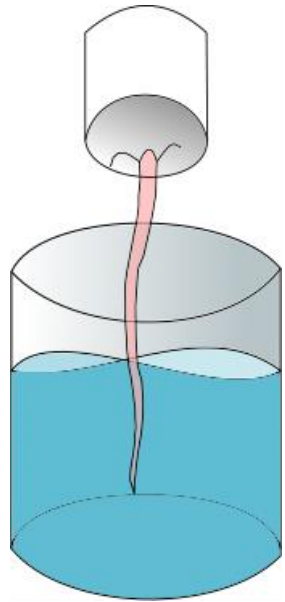


Are our drugs better than morphine?

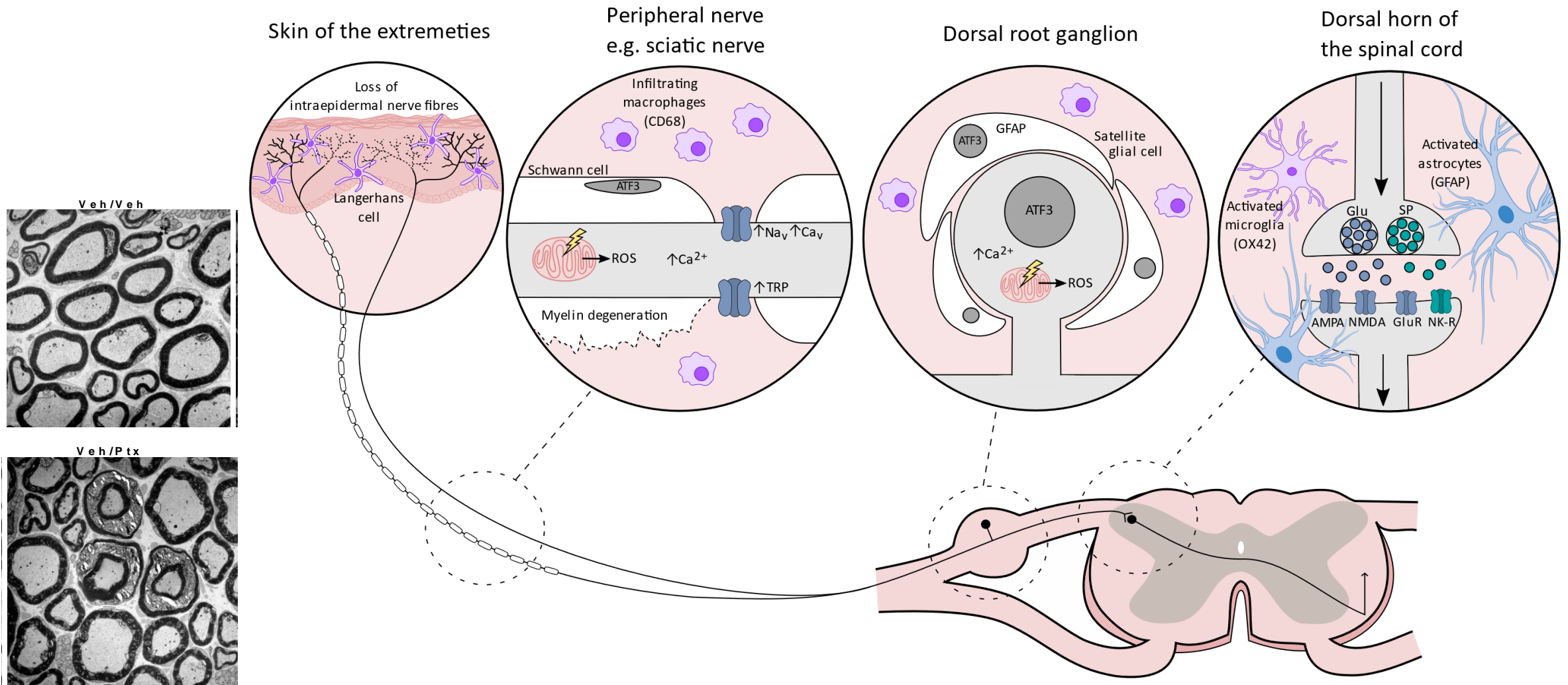


Amy Alder
PhD student

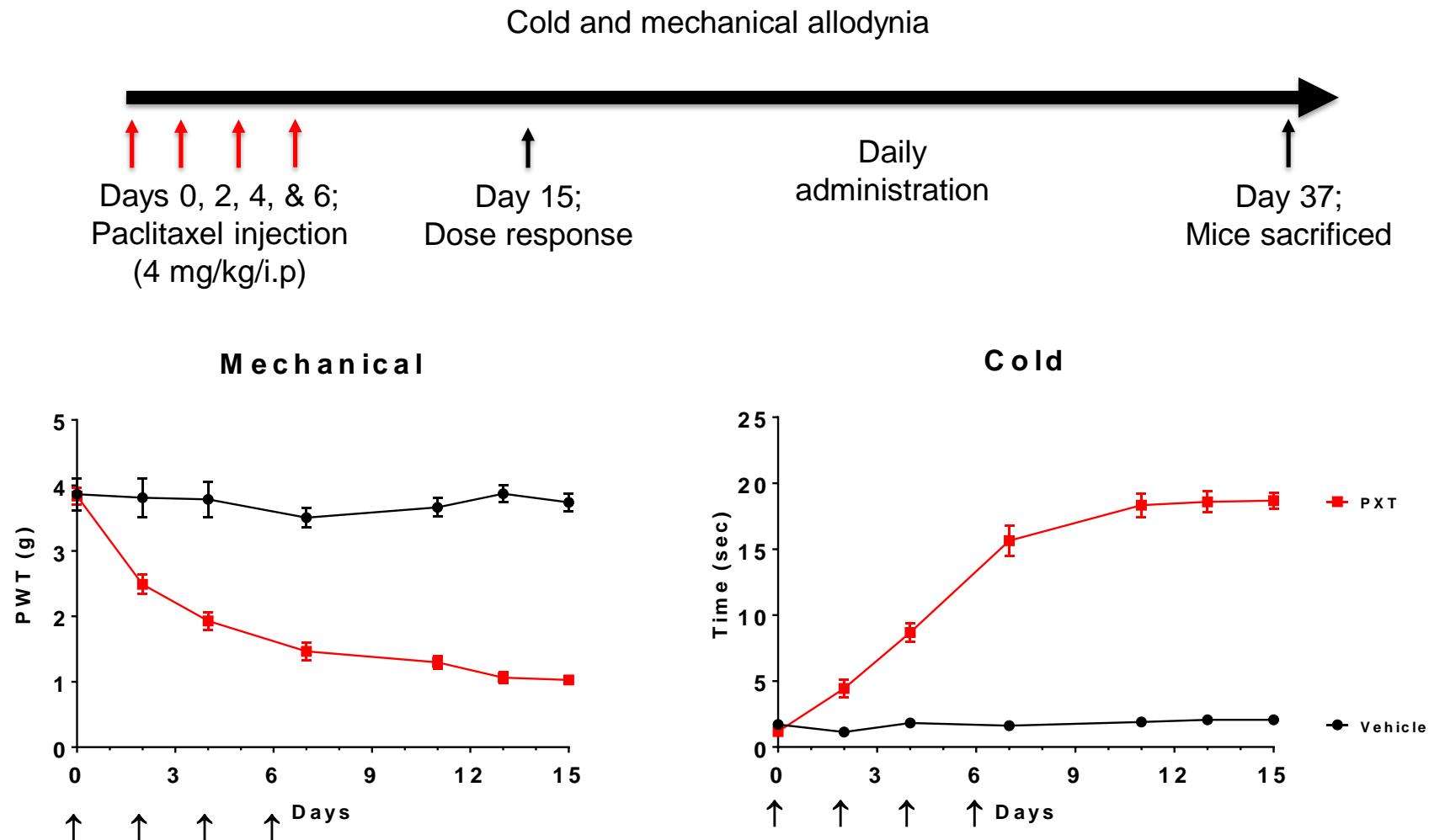
Our drugs have reduced tolerance



Chemotherapy induced neuropathic pain

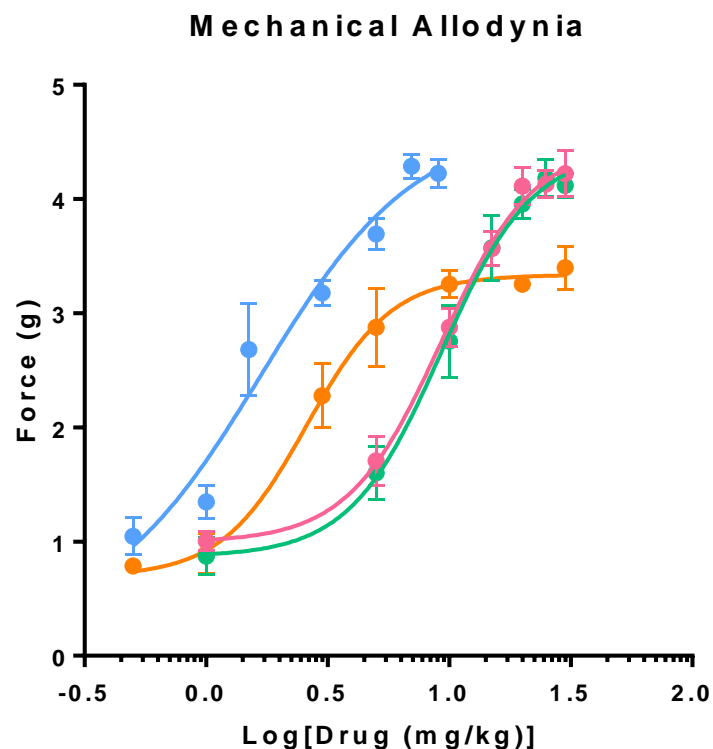


Chemotherapy induced neuropathic pain

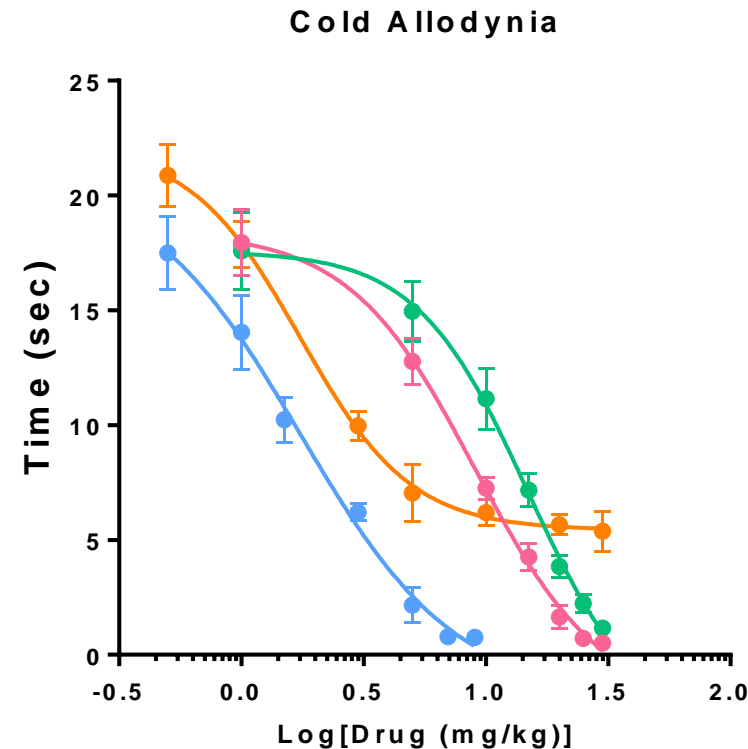


(n = 6 per group)

More potent than current medications



	ED ₅₀ (mg/kg)	ED ₈₀ (mg/kg)
Morphine	9.2	17.2
Gabapentin	2.5	4.45
Kurkinorin	9.2	16.8
Kurkinol	1.6	4.6



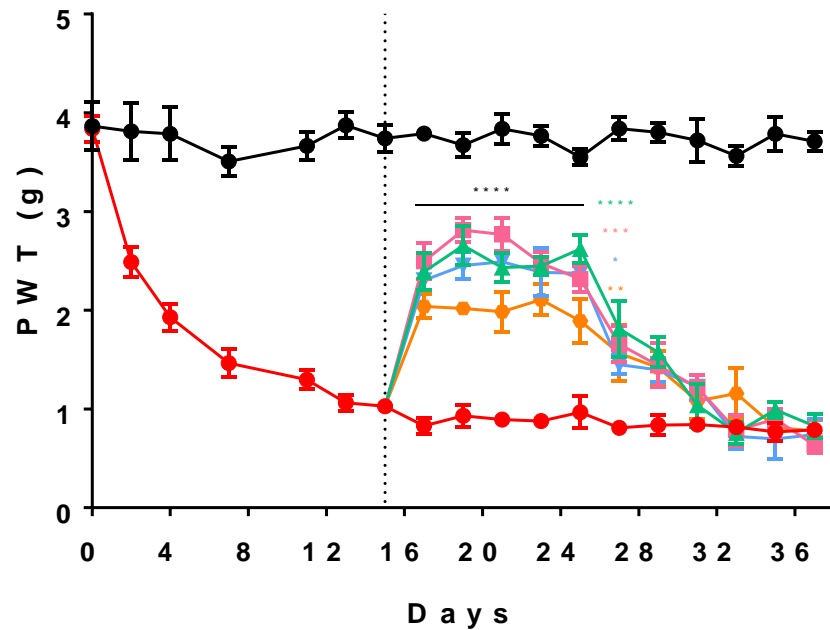
	ID ₅₀ (mg/kg)	ID ₈₀ (mg/kg)
Morphine	9.0	20.6
Gabapentin	1.7	3.5
Kurkinorin	14.8	30.6
Kurkinol	1.7	4.9

(n = 6 per group)

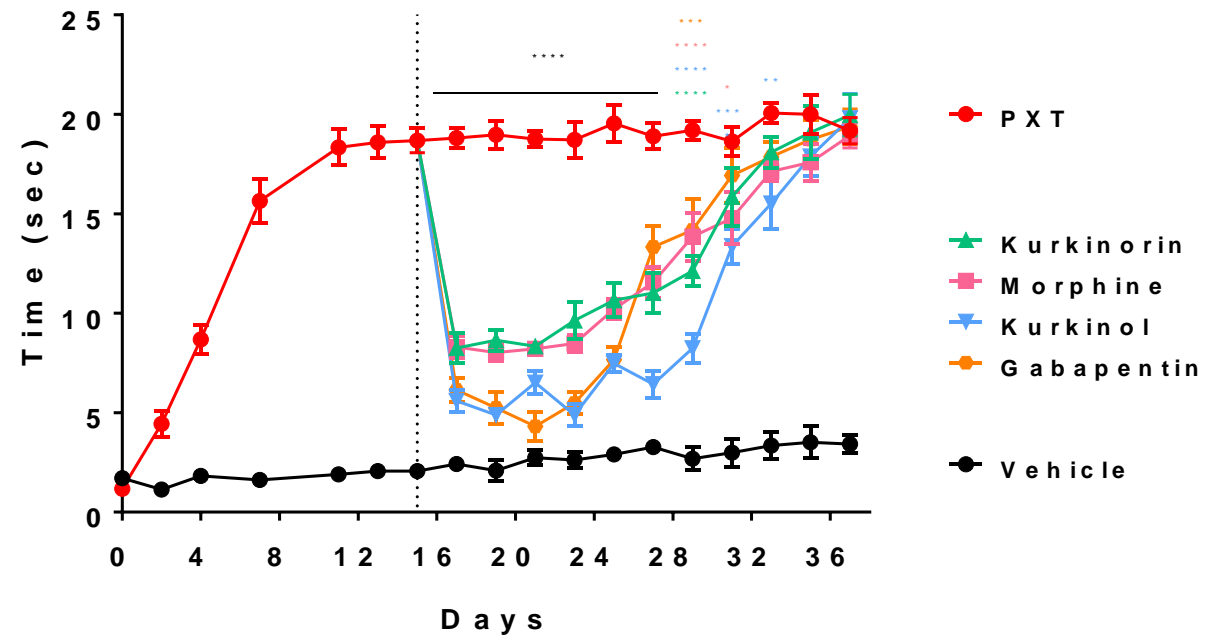
Tolerance remains



Mechanical Allodynia

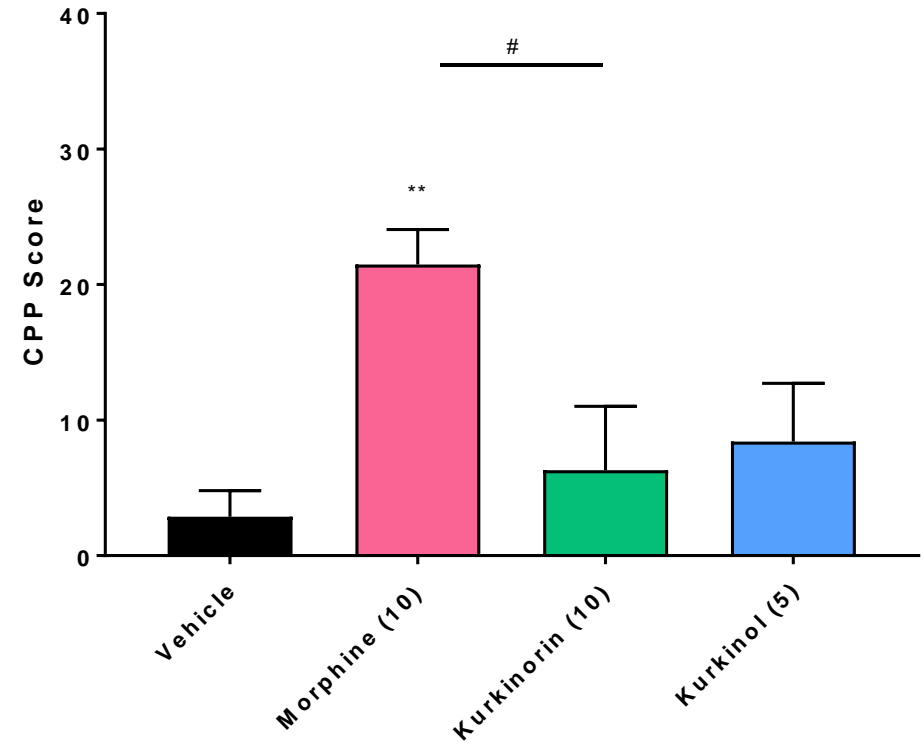
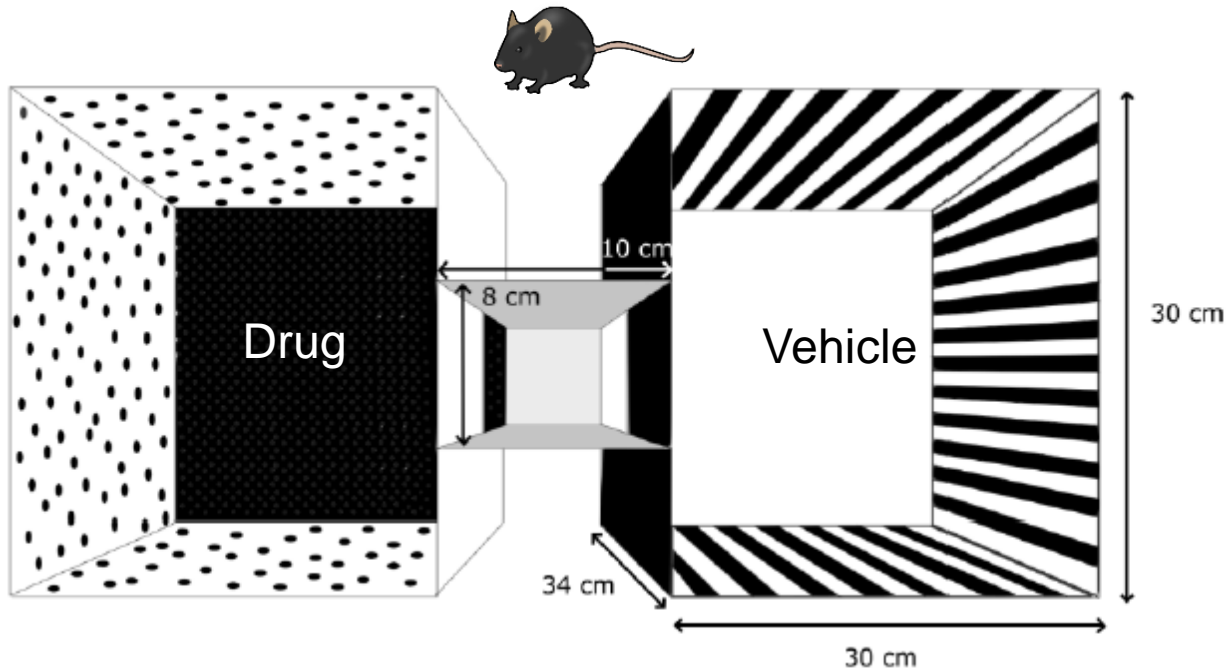
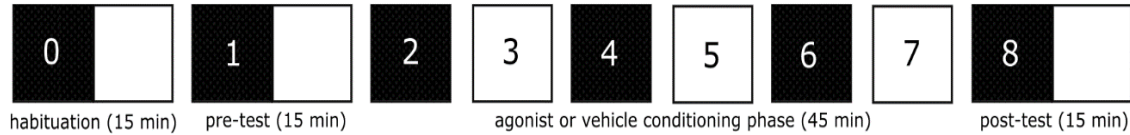


Cold Allodynia



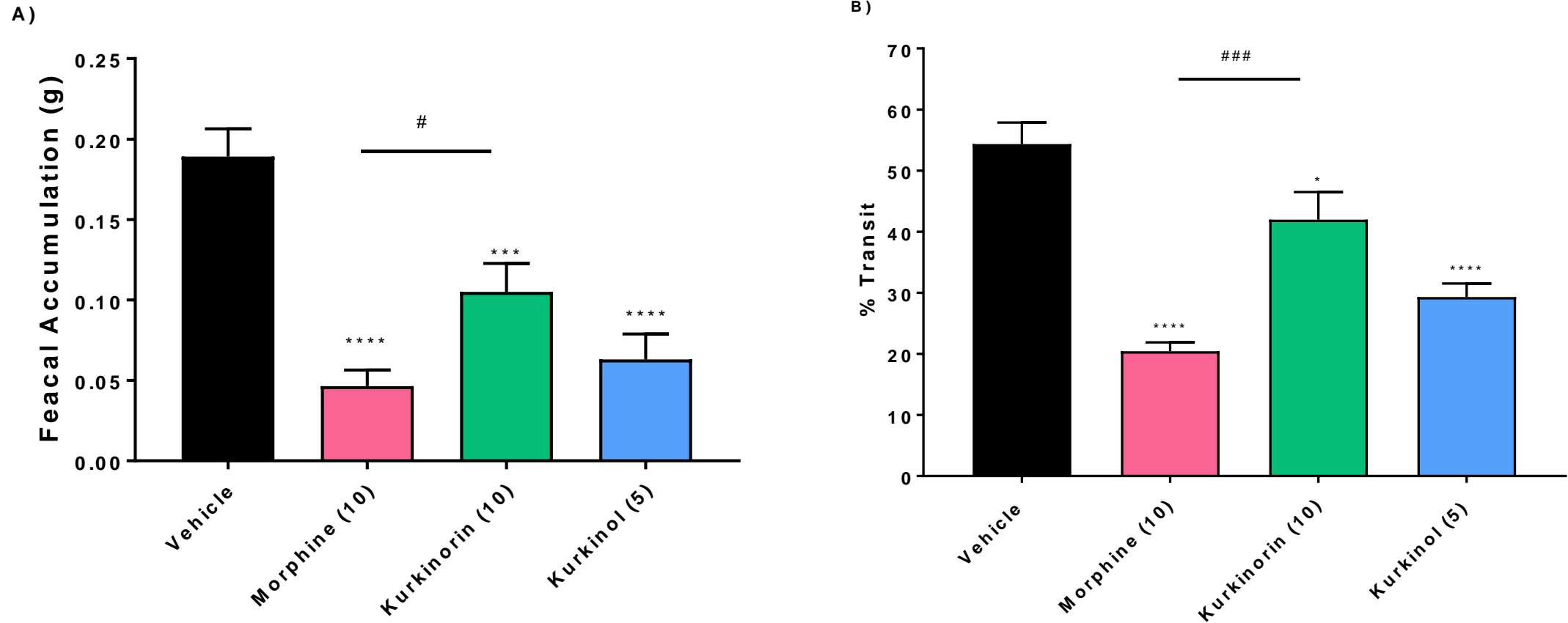
Kurkinorin and Kurkinol have reduced abuse potential

black textured floor white smooth floor



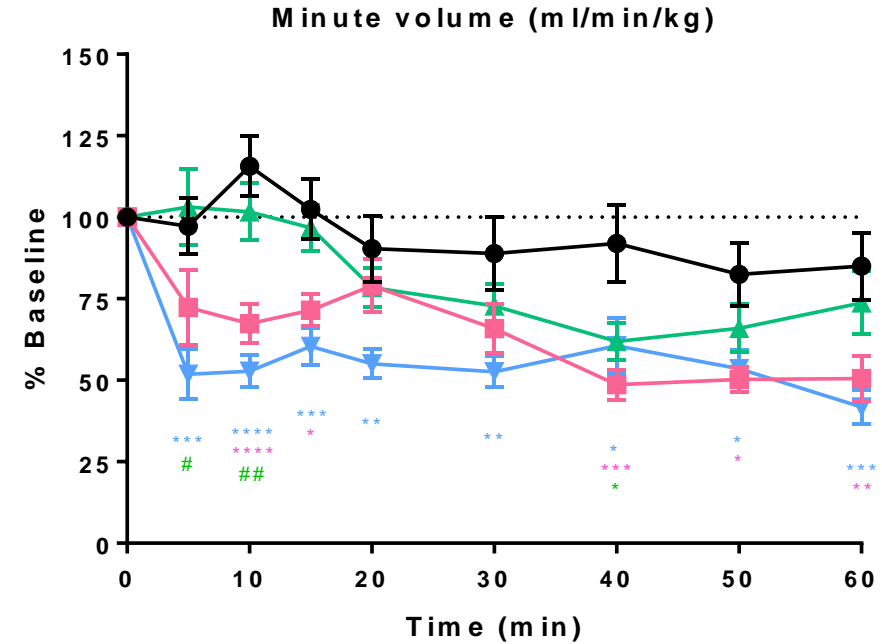
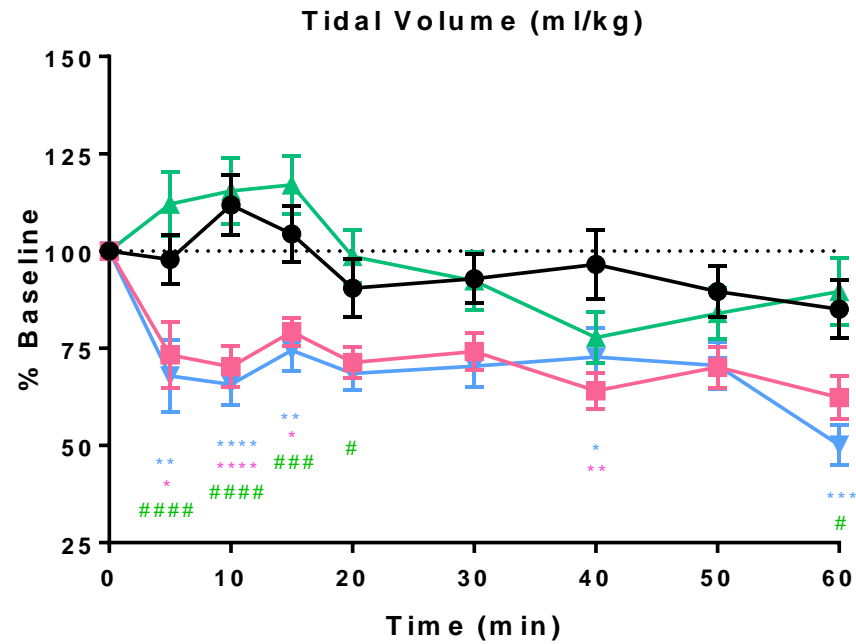
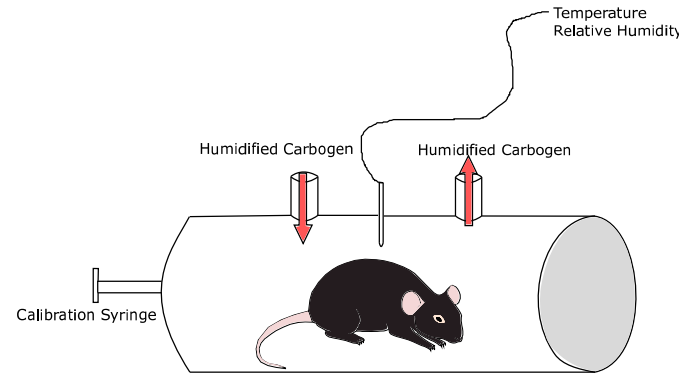
(n= 10-14 per group)

Kurkinorin has reduced inhibition of gut motility



(n= 10-14 per group)

Kurkinorin has no effect on respiration



● Vehicle ▲ Kurkinorin (5)
■ Morphine (5) ▼ Kurkinol (2.5)

(n= 10-14 per group)

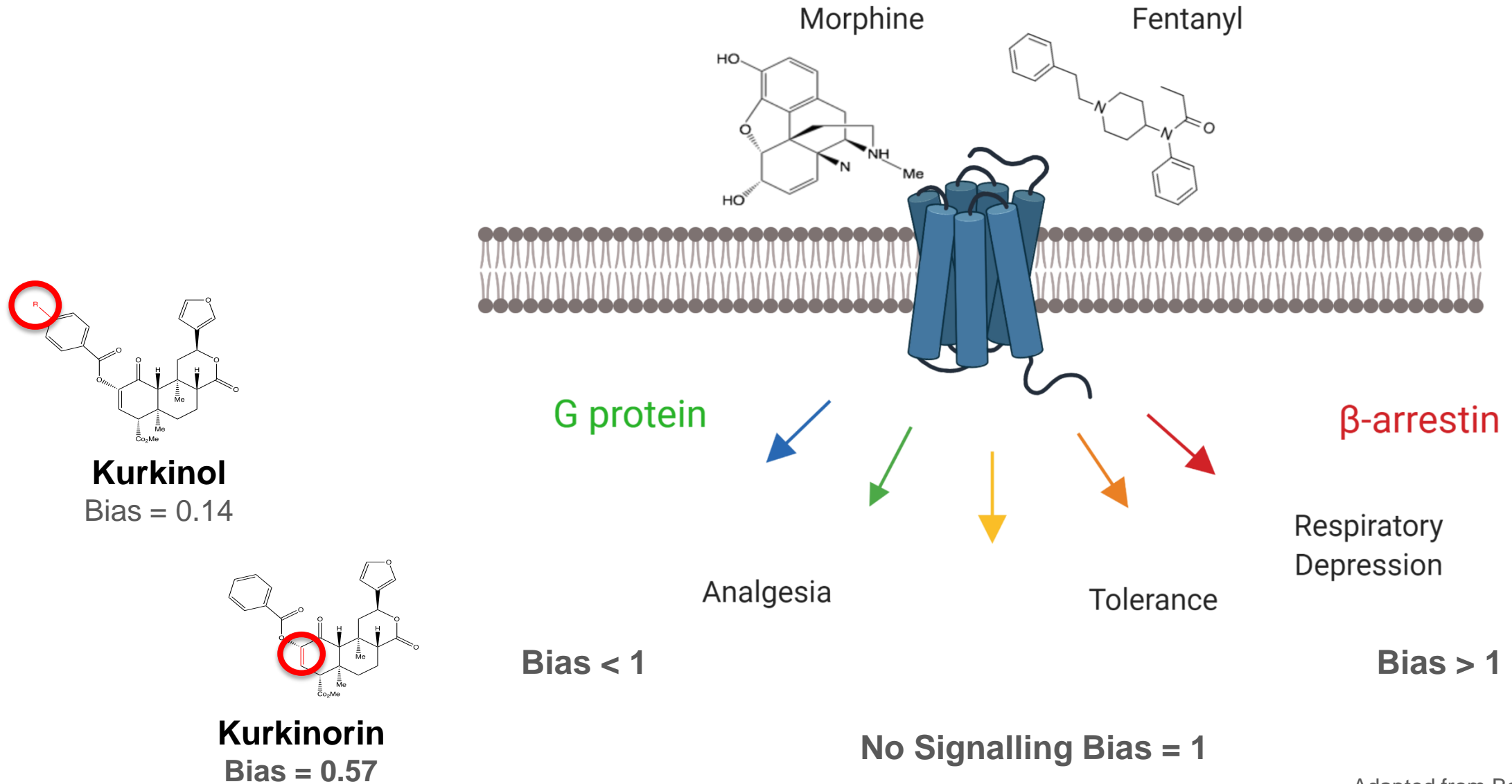
Summary

Bias Factor: 0.57

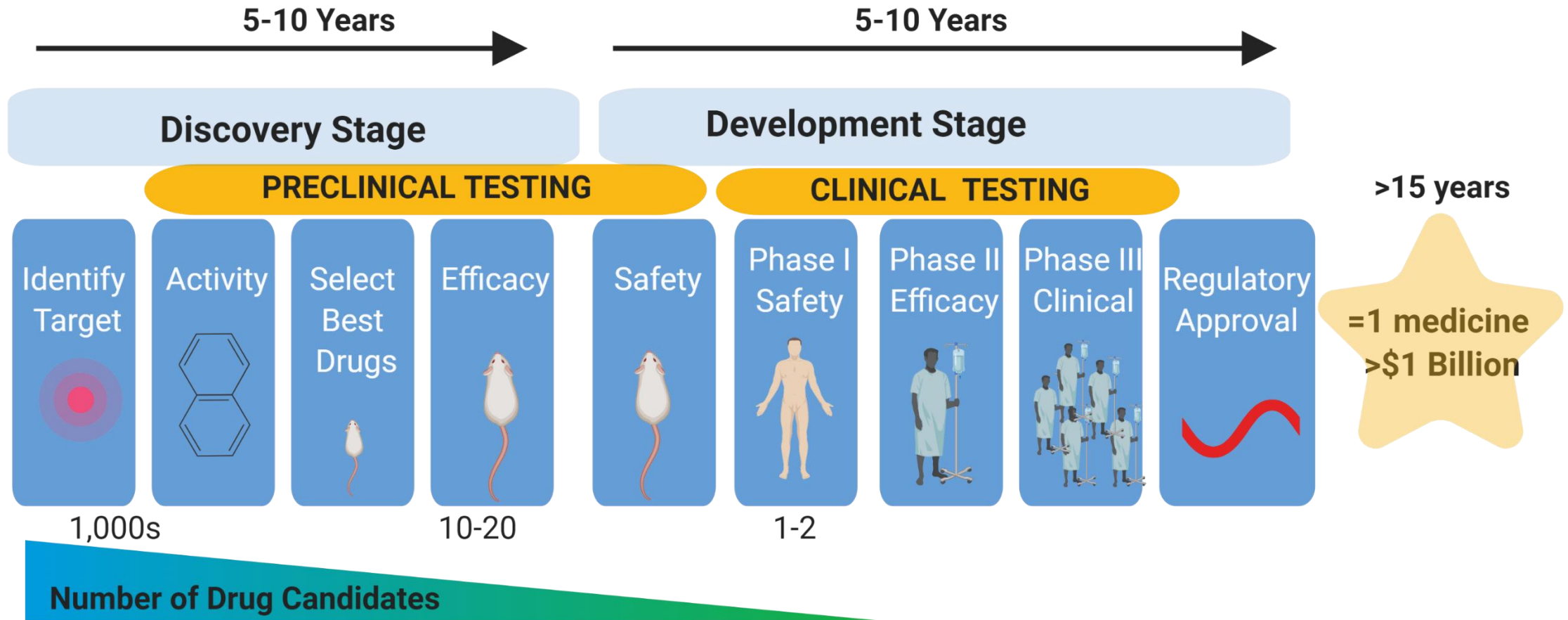
Bias Factor: 0.14

Morphine		Kurkinorin		Kurkinol	
Potent Analgesic	✓	Equipotent to Morphine	✓	More Potent than Morphine	✓✓
Significant Tolerance	✗	Reduced Tolerance	✓	No Tolerance	✓
Significant Constipation	✗	No Significant Constipation	✓	Reduced Constipation	✗
Severe Motor Coordination	✗	Reduced Motor Coordination	✓	Reduced Motor Coordination	—
High Abuse Liability	✗	Reduced Abuse Liability	✓	Reduced Abuse Liability	✓
Respiratory Depression	✗	Very Little change	✓	Respiratory Depression	✗

More complicated than just signalling bias



Drug development pathway

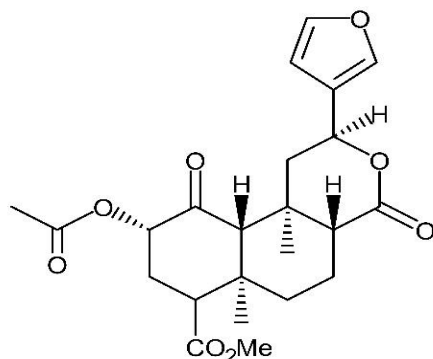
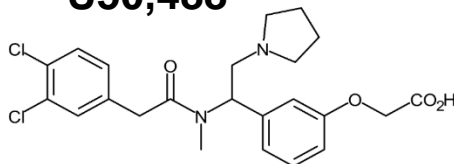


Novel kappa opioid agonists



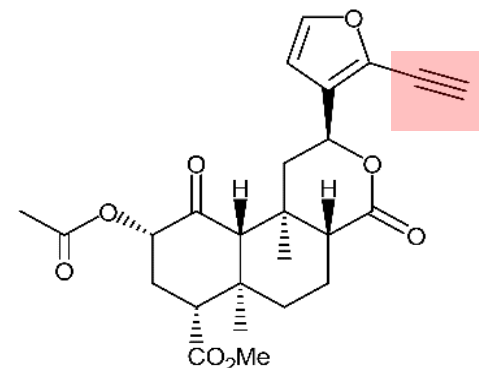
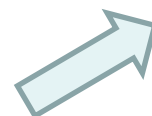
Prof. Tom Prisinzano

U50,488



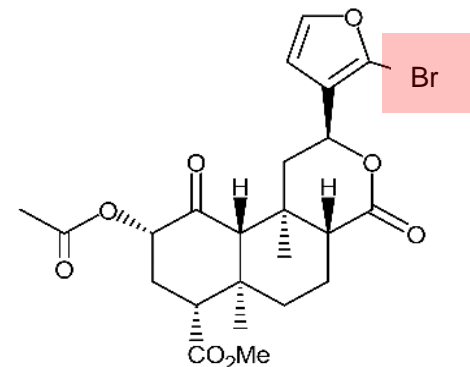
Salvinorin A

$EC_{50} = 0.030 \pm 0.004$ nM



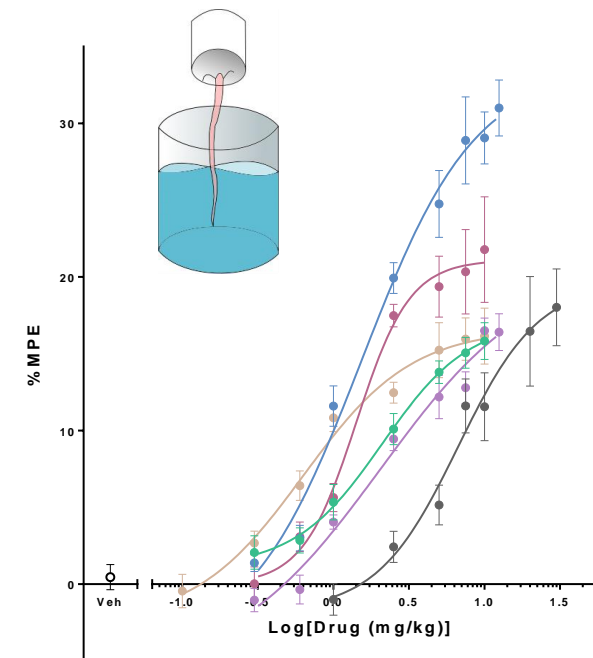
16-Ethynyl Sala

$EC_{50} = 0.019 \pm 0.004$ nM

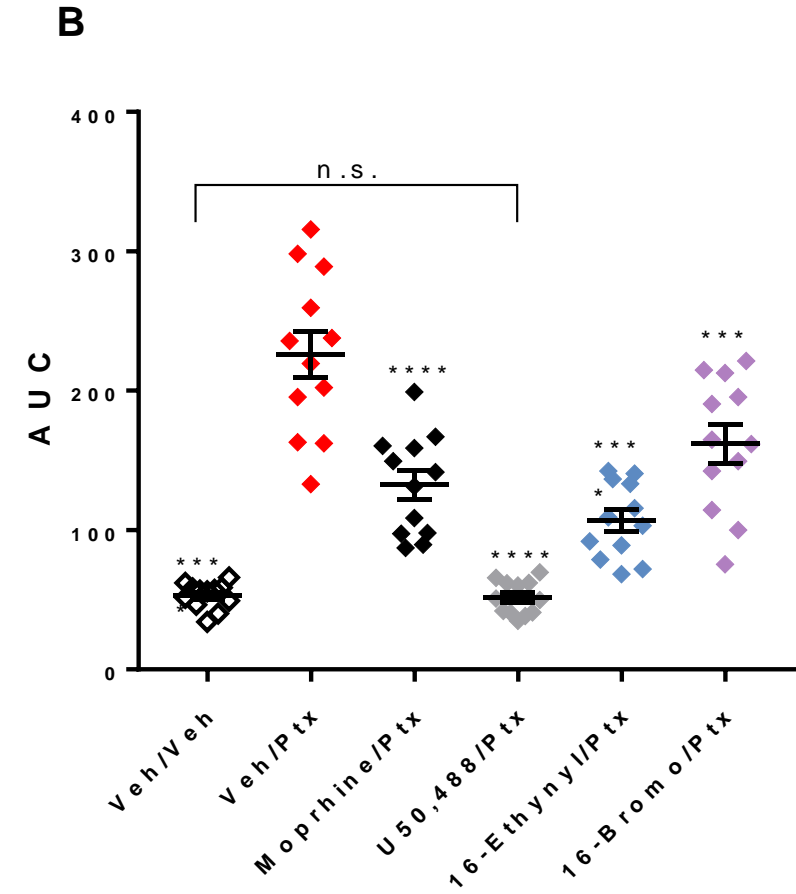
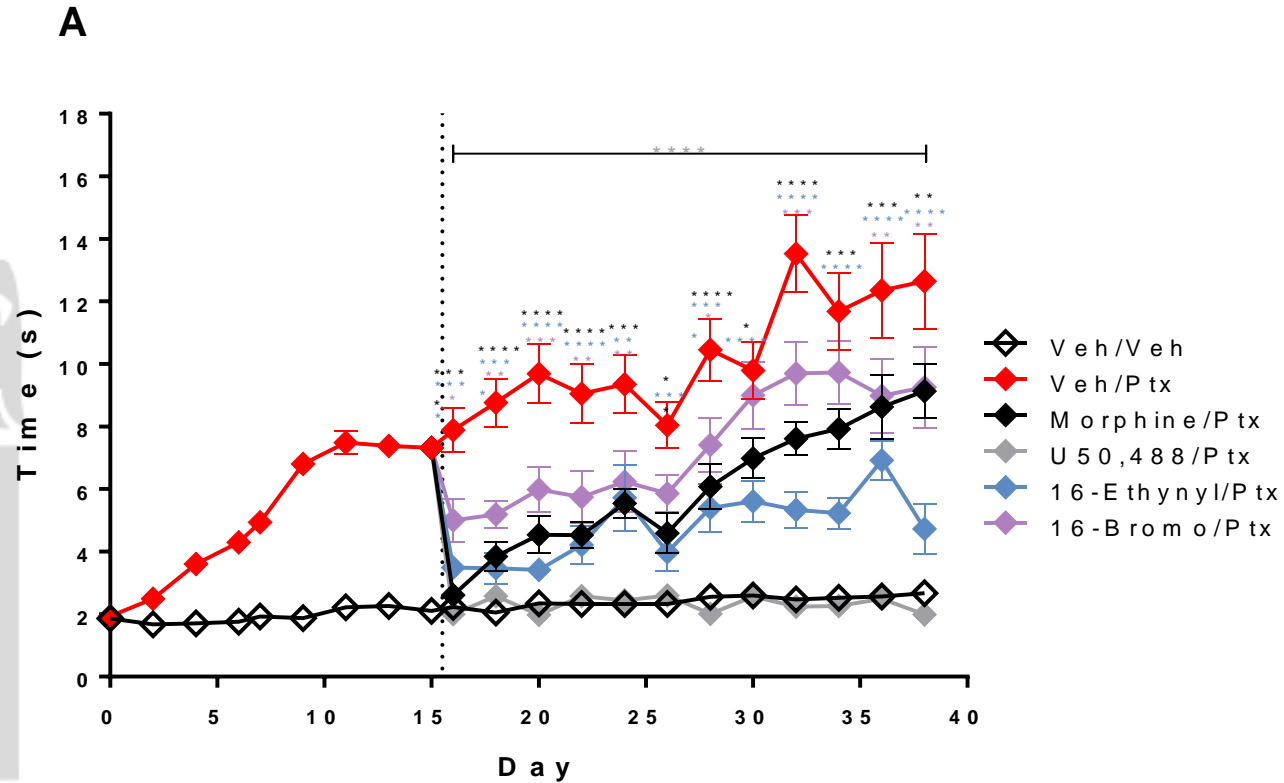


16-Bromo Sala

$EC_{50} = 0.040 \pm 0.010$ nM

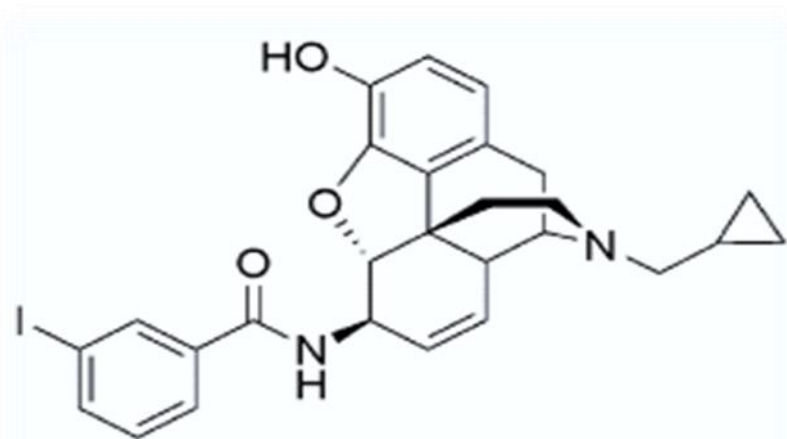


Chemotherapy-induced neuropathic pain



Do mixed opioid KOPr/DOPr agonists improve the side effect profile of selective KOPr agonists?

MP1104



Receptor Binding: KOR>MOR>DOR

K_i [nM]			
	MOR-1	KOR-1	DOR-1
MP1104	0.021 ± 0.003	0.0064 ± 0.002	0.08 ± 0.019
U50,488		0.73 ± 0.32	

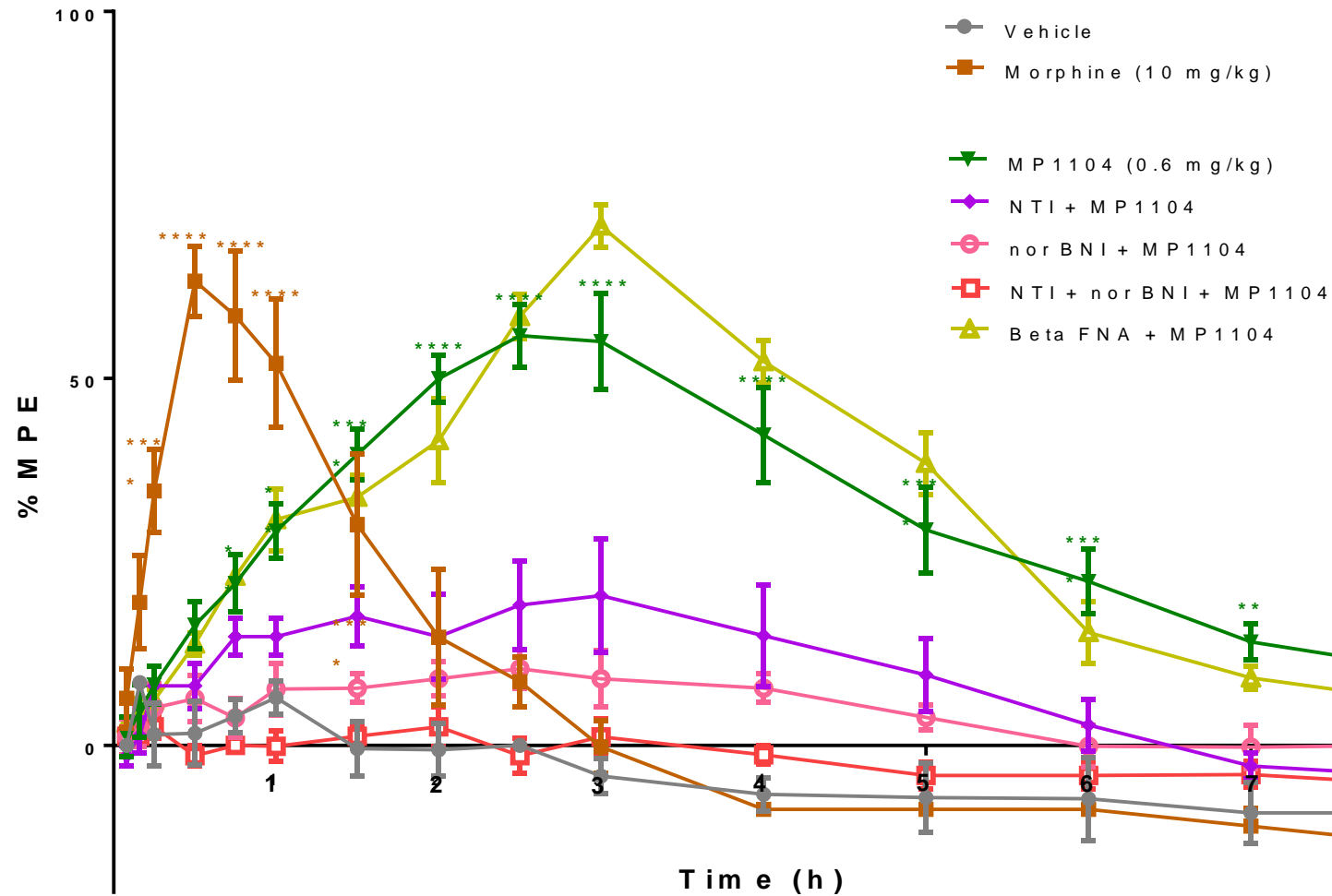


Dr Susruta Majumdar

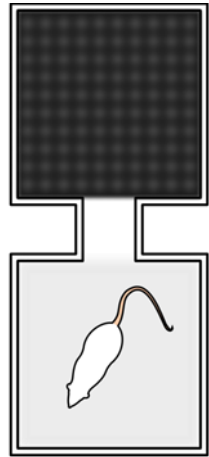
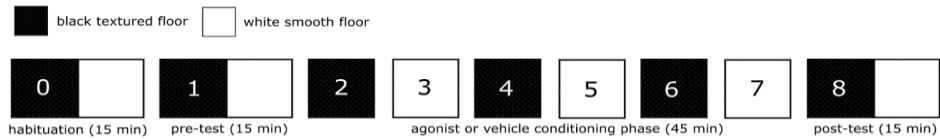


R. Uprety and
GW, Pasternak

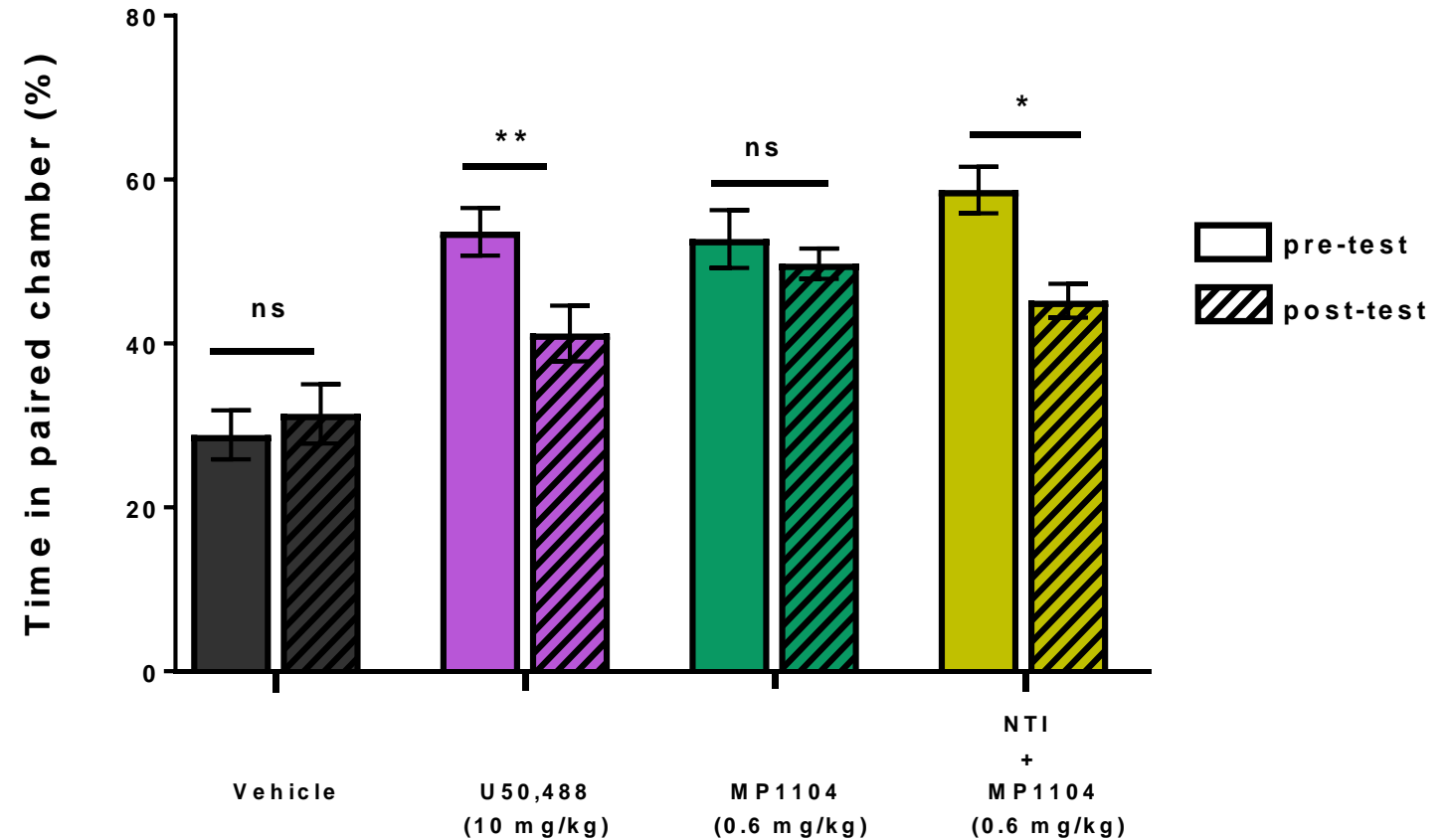
Antinociceptive effects are KOPr and DOPr mediated



Aversive effects are attenuated via DOPr agonist effects



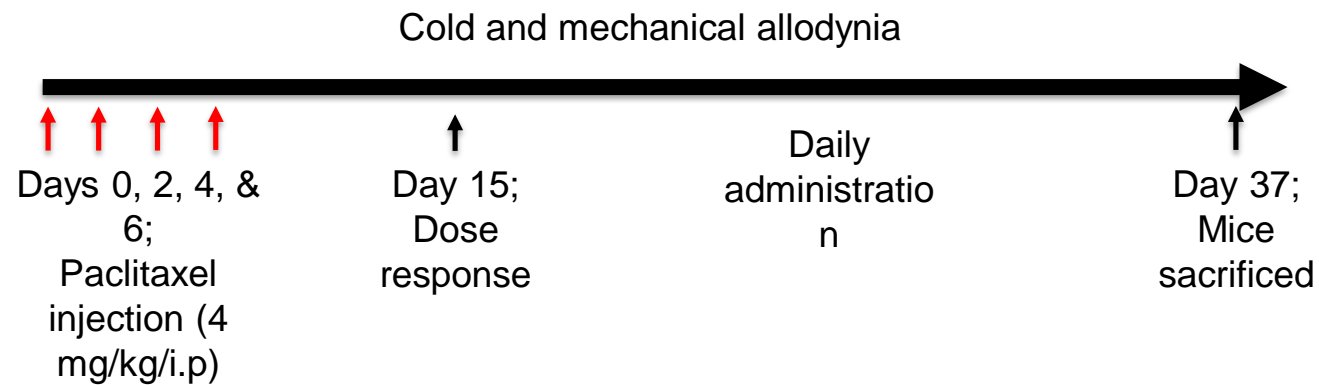
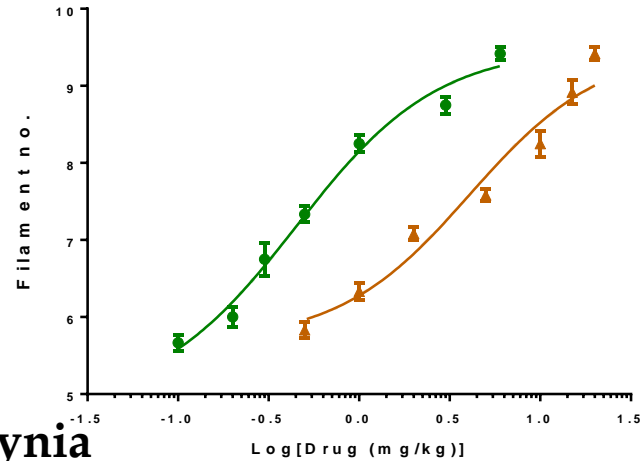
Conditioned Place Aversion



Chronic MP1104 treatment effects on Neuropathic pain

Drug	ED ₅₀ value (mg/kg)
MP1104	0.45
Morphine	4.07

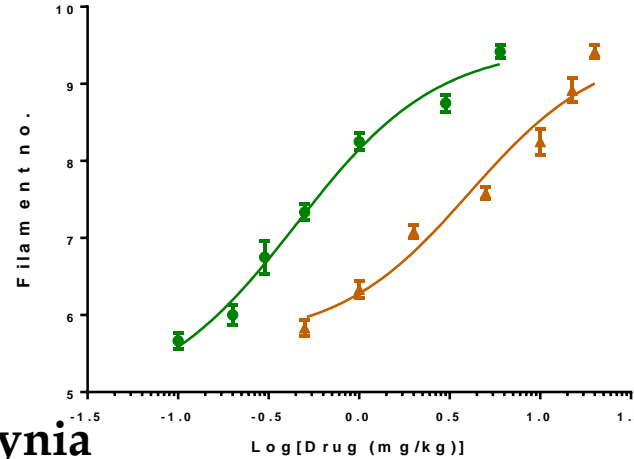
Mechanical allodynia



Chronic MP1104 treatment effects on Neuropathic pain

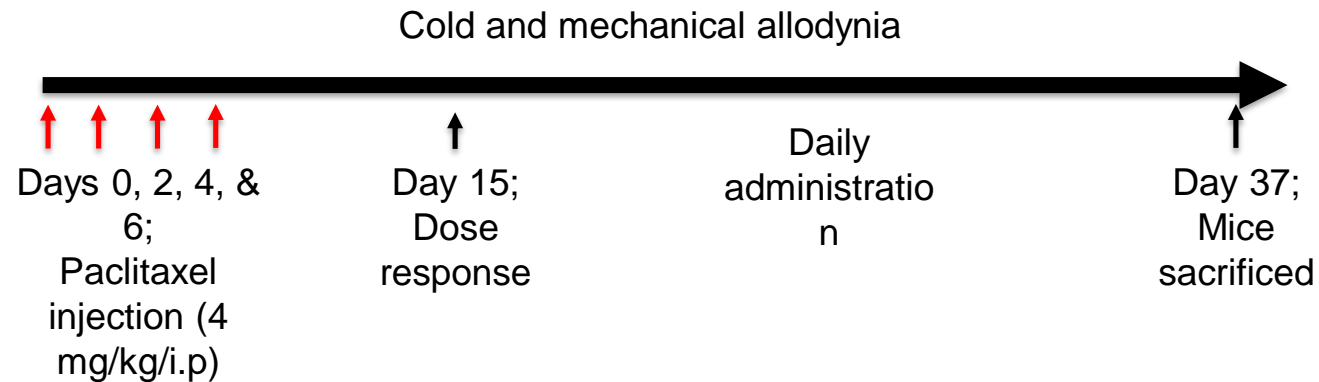
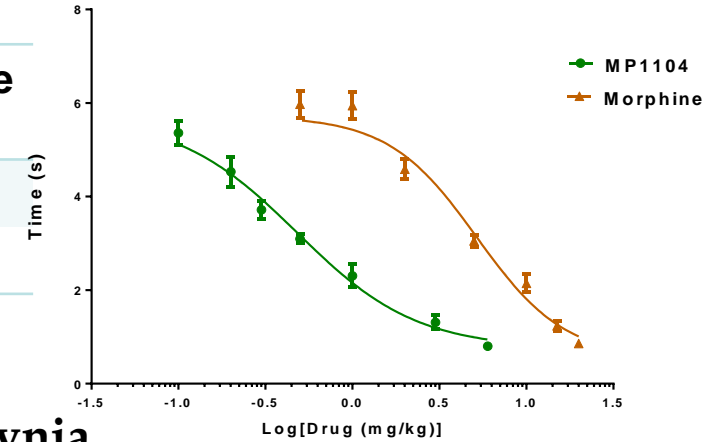
Drug	ED ₅₀ value (mg/kg)
MP1104	0.45
Morphine	4.07

Mechanical allodynia



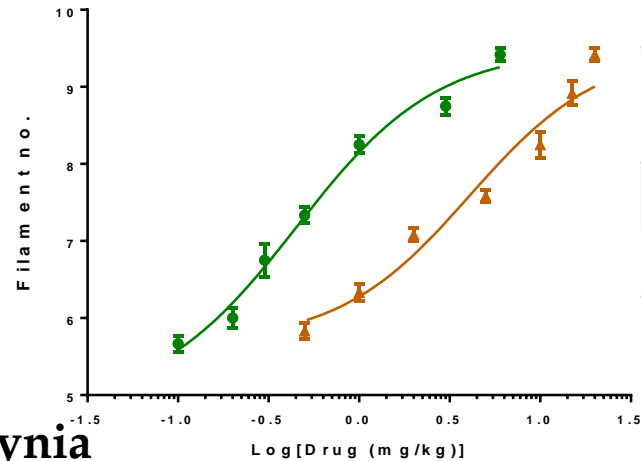
Drug	ID ₅₀ value (mg/kg)
MP1104	0.47
Morphine	5.18

Cold allodynia

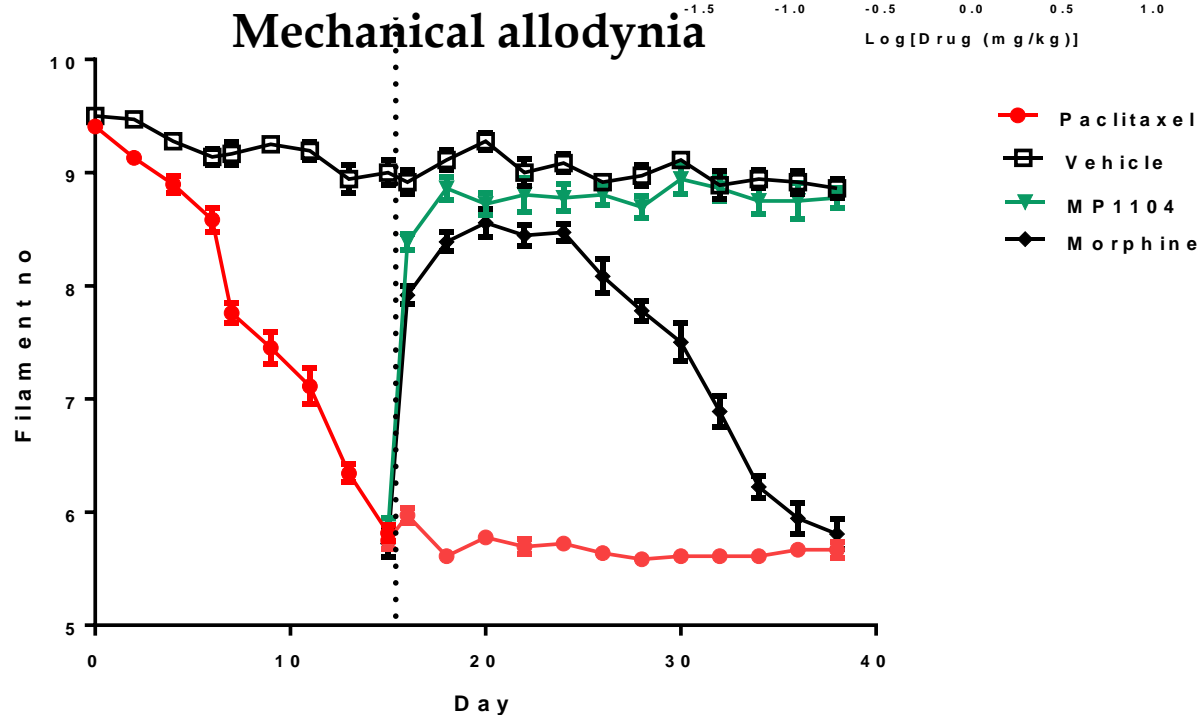
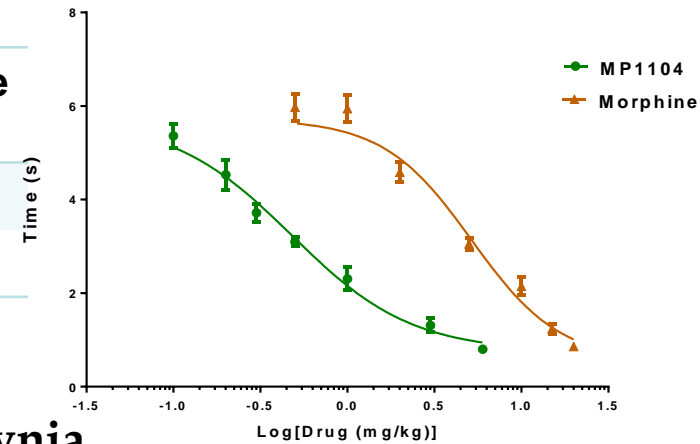


Chronic MP1104 treatment effects on Neuropathic pain

Drug	ED ₅₀ value (mg/kg)
MP1104	0.45
Morphine	4.07



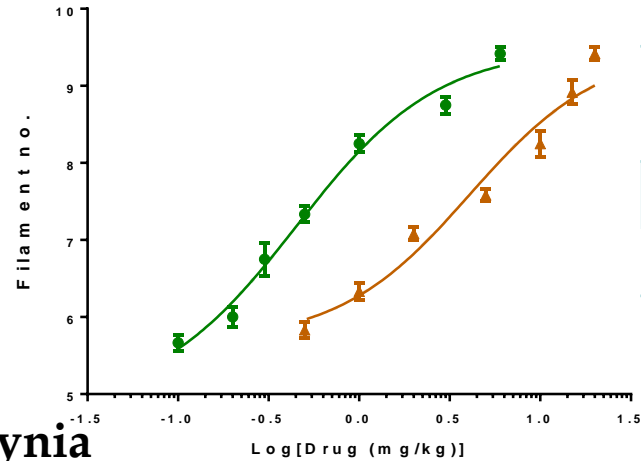
Drug	ID ₅₀ value (mg/kg)
MP1104	0.47
Morphine	5.18



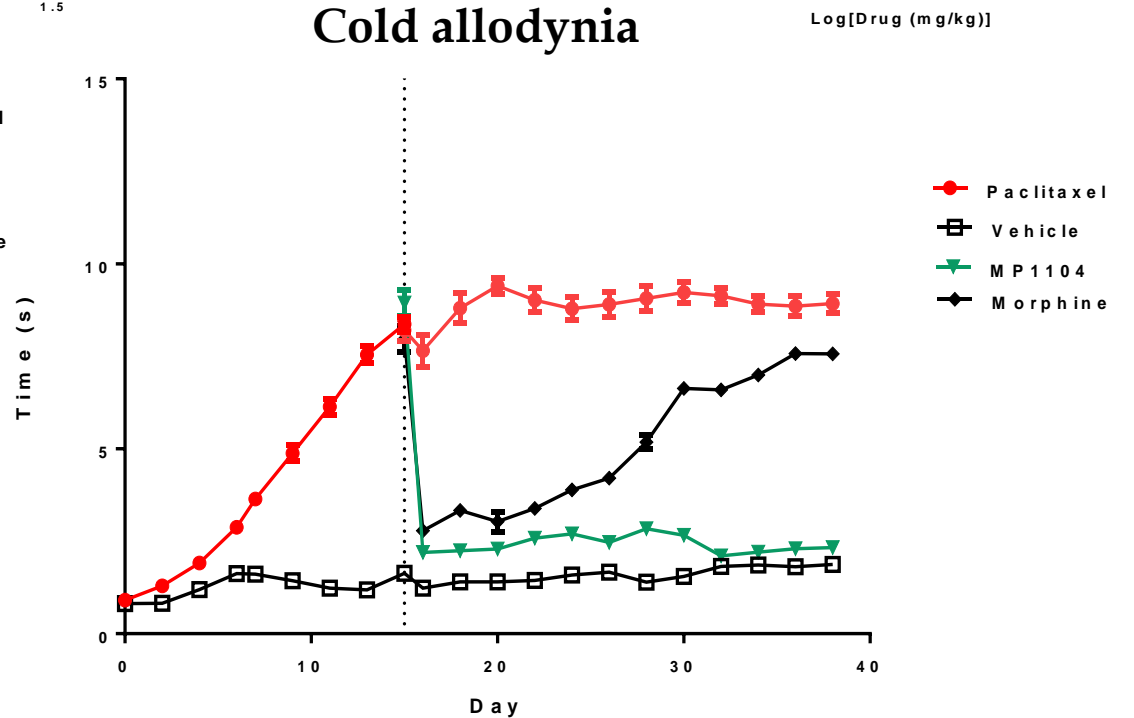
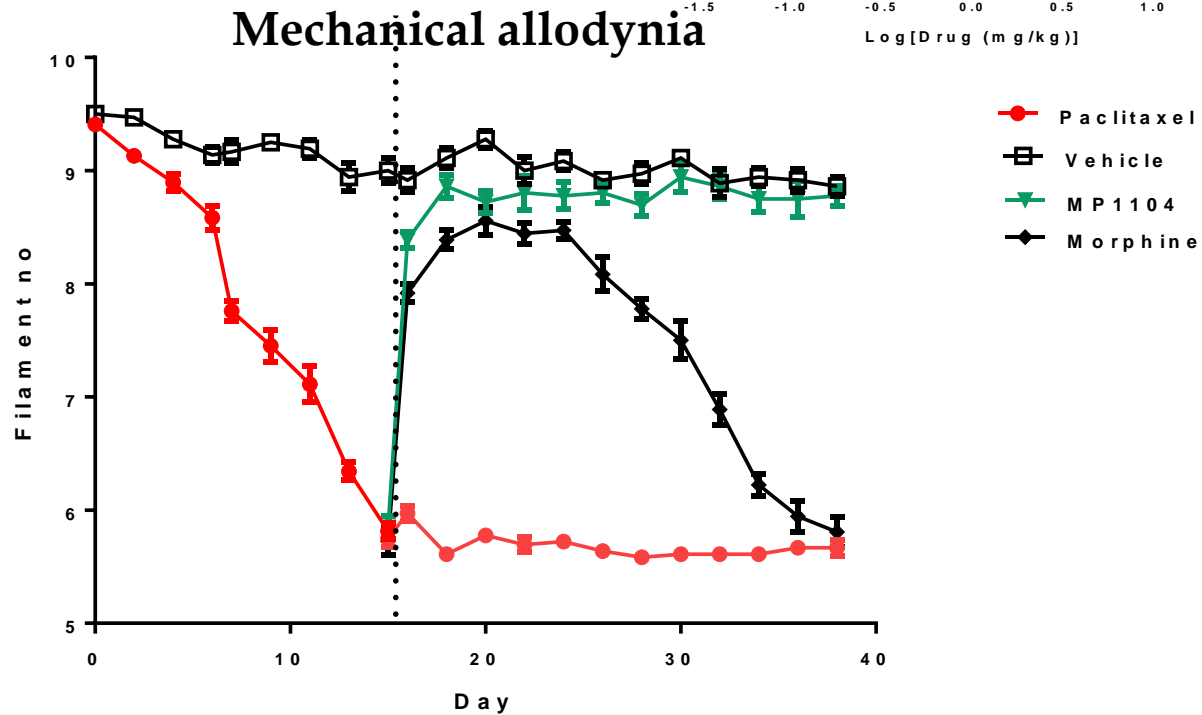
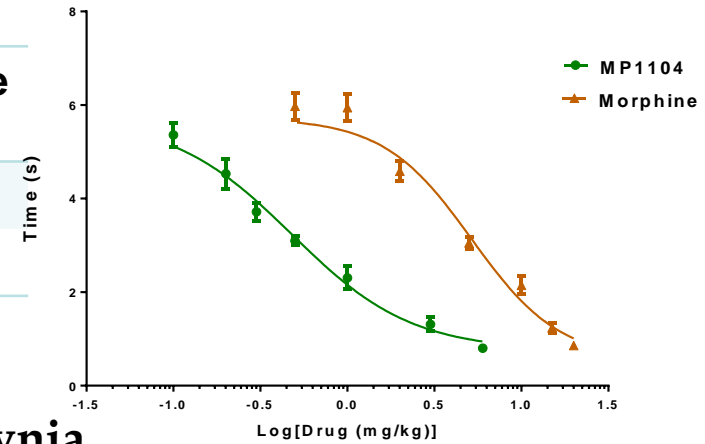
Cold allodynia

Chronic MP1104 treatment effects on Neuropathic pain

Drug	ED ₅₀ value (mg/kg)
MP1104	0.45
Morphine	4.07



Drug	ID ₅₀ value (mg/kg)
MP1104	0.47
Morphine	5.18

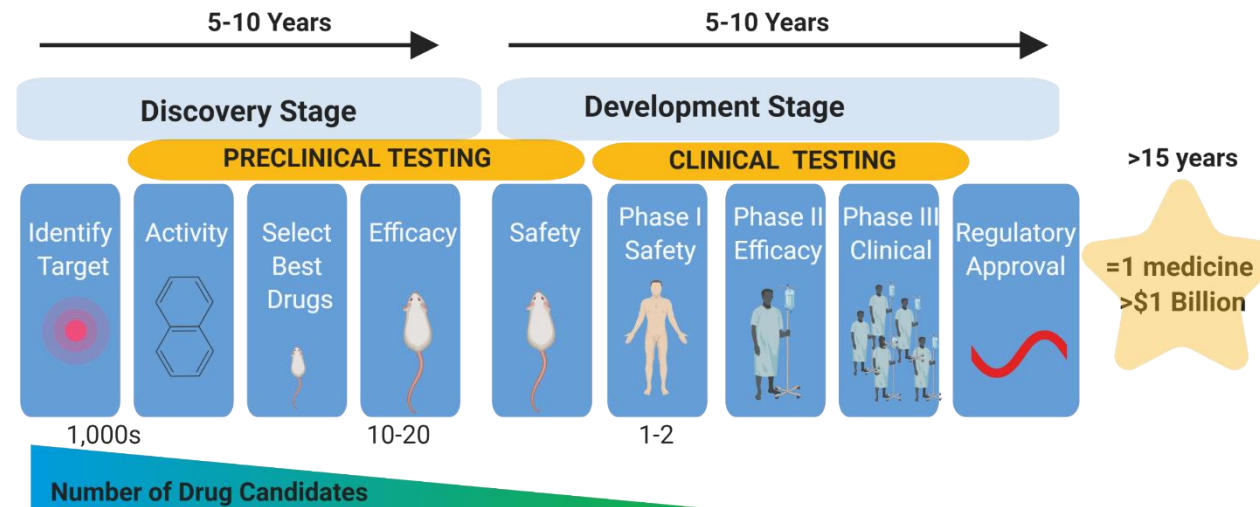


Research strategies to combat chronic pain

1. Are there better drug targets? **YES**

2. Can we make better drugs to existing targets?

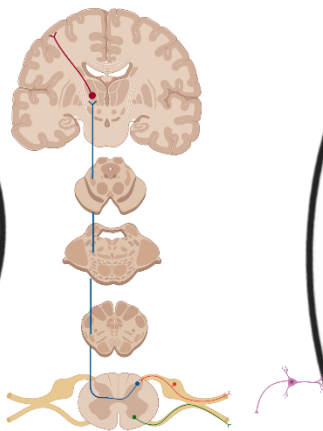
YES



Research strategies to combat chronic pain

1. Are there better drug targets?

Conotoxins



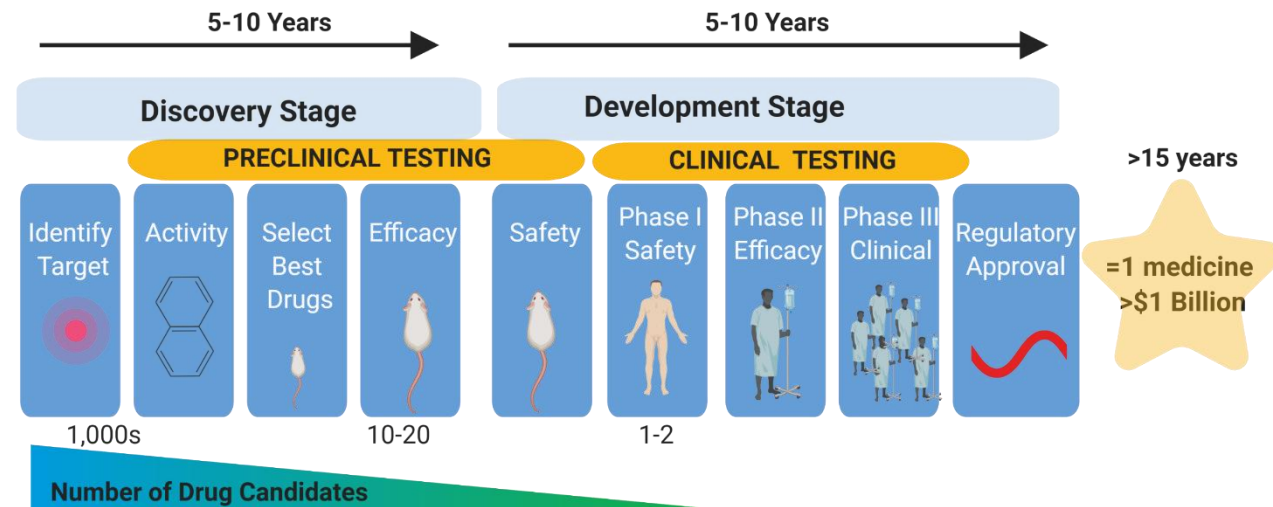
Peptide	Amino Acid Sequence	Target
ω -MVIIA	CKGKGAKCSRLMYDCCTGSCRSKGK*	Ca ²⁺ channel (N-type)
ω -CVID	CKSKGAKCSKLMYDCCSGSCSGTVGRC*	Ca ²⁺ channel (N-type)
Conantokin-G	GEyyLQyNQyLIRyKS N*	NMDAR (NR2B)
Contulakin-G	ZSEEGGSNATKKPY IL	Neurotensin receptor
α -Vc1.1	GCCSDPRCNYDHP EIC*	nAChR (α 9 α 10)
χ -MrlA	NGVCCGYKLCHOC	Norepinephrine transporter



Research strategies to combat chronic pain

1. Are there better drug targets? **YES**

2. Can we make better drugs to existing targets? **YES**

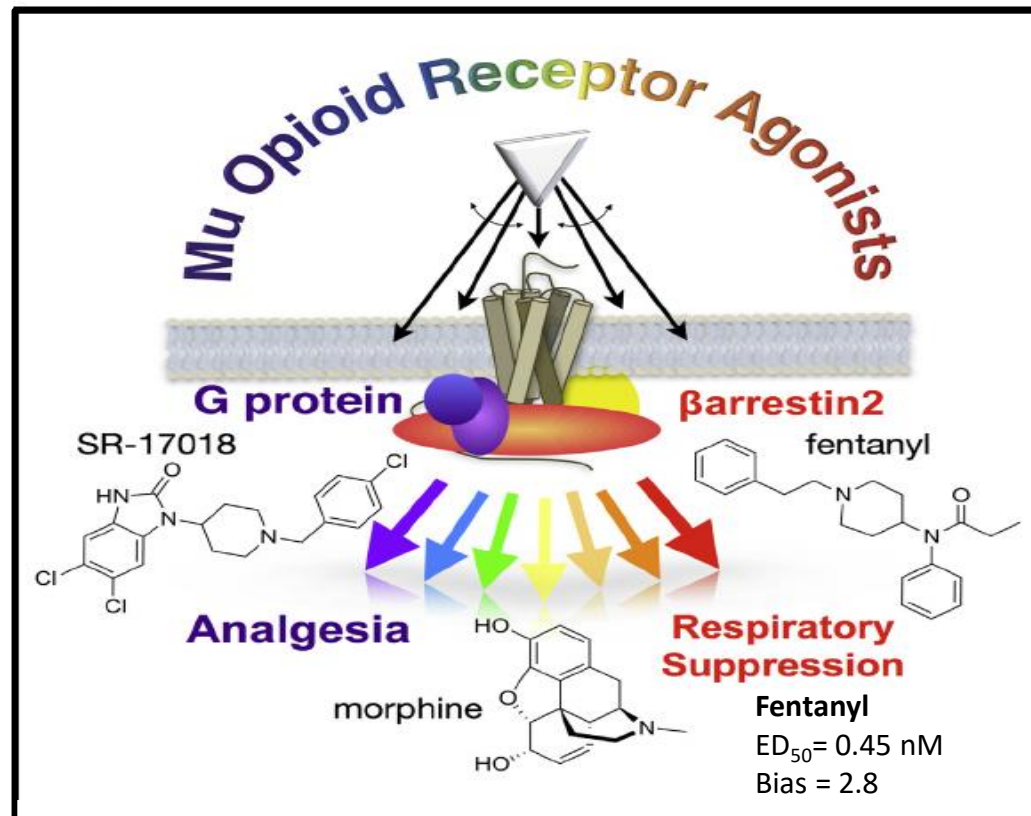


Do G-protein biased opioid mu-opioid agonists make better, safer pain medications?

Cell

Bias Factor and Therapeutic Window Correlate to Predict Safer Opioid Analgesics

Graphical Abstract (2017)



Authors

Cullen L. Schmid, Nicole M. Kennedy, Nicolette C. Ross, ..., Michael D. Cameron, Thomas D. Bannister, Laura M. Bohn

Correspondence

lbohn@scripps.edu

In Brief

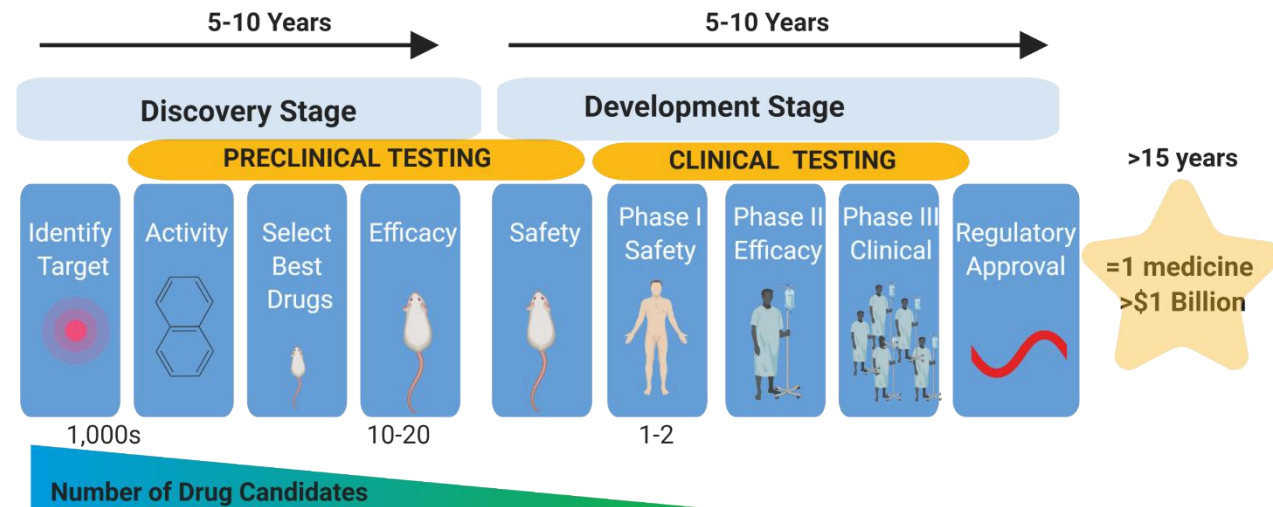
Exploiting ligand bias enables the design of new opioid receptor ligands aimed at reducing side effects.

- *TRV130 (oliceridine) Trevena*
- *PZM21: Gai-biased MOPr ligand*

Research strategies to combat chronic pain

1. Are there better drug targets? **YES**

2. Can we make better drugs to existing targets? **YES**



Acknowledgements

Victoria University of Wellington

- Dr Kelly Paton
- Amy Alder
- Nitin Kumar
- Mohan Permual
- Richard Anderson
- Dr Miguel Biscaia
- Dr Andy Biggerstaff
- Dr Diana Atigari
- Dr Amy Ewald
- Aimee Culverhouse
- David Young
- Stephen Matthews
- Susan Welsh
- Afnan Al Abadey
- Dr Nikki Templeton
- Kendra Boyes



The University of Kansas/Kentucky

- Prof. Thomas Prisinzano
- Dr Rachel Saylor Crowley
- Dr Andrew Riley
- Samuel Williamson



Health Research
Council of
New Zealand

